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ORIGINAL ARTICLES

INTRACELLULAR MAGNESIUM IN DELIRIUM TREMENS AND UREMIA

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A deficiency or excess of magnesium as an etiologic factor in certain clinical symptoms of man has not been universally accepted despite a number of affirmative reports in the literature (Flink[2], Flink *et al.*[3], Hamburger[4], Hammarsten and Smith[5,8,9,10], Hirschfelder[6], Suter and Klingman[11], Wacker and Vallee[12]). It is true, for example, that not all patients with delirium tremens have abnormally low serum magnesium values. Indeed, exceedingly low serum values are found in only about 50% of the cases (Flink[2], Smith and Hammarsten[10]). It is also true that low serum magnesium values have been found in some hospitalized patients who do not manifest the clinical picture associated with the "magnesium deficiency syndrome" (Flink[2], Suter and Klingman[11]). Serum magnesium values above the normal range are found in some patients with asymptomatic azotemia, but exceedingly high values almost invariably occur only in uremic patients with central nervous system depression (Smith and Hammarsten[8]).

The seemingly inconsistent results of serum magnesium studies are not unlike early results published on potassium. In the final analysis it seems more reasonable that the total body content of the cation is the important consideration. Magnesium is predominantly an intracellular cation and its known biological effects are produced within the cell. Perhaps, then, measurement of intracellular fluid magnesium might better reflect a functional deficiency or excess than its extracellular counterpart, the serum. It is the purpose of this paper to report such intracellular measurements in patients with delirium tremens and uremia. Since erythrocytes are the only easily obtained body cells, determinations were made on these cells. It is recognized that the erythro-

cyte magnesium concentration does not necessarily reflect that of other body cells.

Material and Methods. Fifteen milliliters of heparinized blood were withdrawn from the patient and separated into 2 equal portions. The plasma was immediately separated from one sample. Magnesium determinations were done on plasma and whole blood by an EDTA spectrophotometric titration method previously described (Carubelli, Smith and Hammarsten[1]). The erythrocyte magnesium concentration was then calculated from these data and the hematocrit. As previously reported the method yielded satisfactory recoveries and duplicate determinations were also satisfactory.

Results. HEALTHY ADULTS. Erythrocyte magnesium determinations were done on 13 healthy adults. As reported previously (Carubelli, Smith and Hammarsten[1]) the mean erythrocyte magnesium concentration was 5.29 ± 0.34 mEq. per L. with a 2 S. D. range of 4.61 to 5.97 mEq. per L. The mean plasma magnesium concentration was 1.80 ± 0.13 mEq. per L. with a 2 S. D. range of 1.54 to 2.06 mEq. per L.

DELIRIUM TREMENS. Twelve patients with delirium tremens have been studied. All of the patients showed disorientation and confusion; 7 of them were obviously hallucinating; and all but one had a pronounced tremor. As shown in the table, the mean plasma magnesium concentration was 1.50 ± 0.28 mEq. per L., significantly lower than the control group. The mean erythrocyte magnesium concentration was 3.9 ± 0.75 mEq. per L., representing a 40% decrease from the control mean.

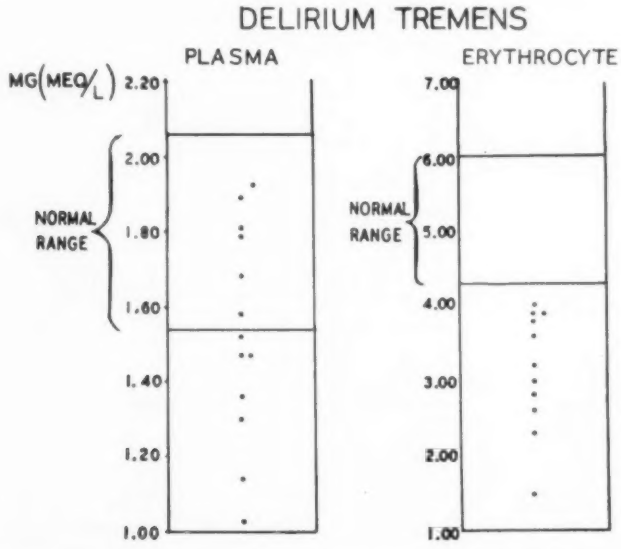

Fig. 1.—Erythrocyte and plasma magnesium values in patients with delirium tremens.

Of greater significance are the data on the individual patient values shown in Fig. 1. Five of the 12 patients had a plasma value within the normal range, whereas the erythrocyte values were abnormally low in all cases.

Nine of the patients were treated with intramuscular magnesium sulfate. Marked improvement was noted in all of them after 12 to 24 hours of therapy.

However, rapidity of improvement was not compared to that of a significant number of patients with delirium tremens not receiving magnesium sulfate. The delay of improvement following magnesium sulfate administration will be discussed further. Repeat magnesium determinations on the treated patients were made 72 hours after institution of the therapy. The mean values within the normal range (Fig. 2), whereas the erythrocyte values were all abnormally elevated.

ELECTROCARDIOGRAMS. Electrocardiograms were made on 3 of the patients with delirium tremens. One showed a nodal tachycardia with frequent premature ventricular systoles; one showed primary T-wave changes; the other was not remarkable. The tracings became

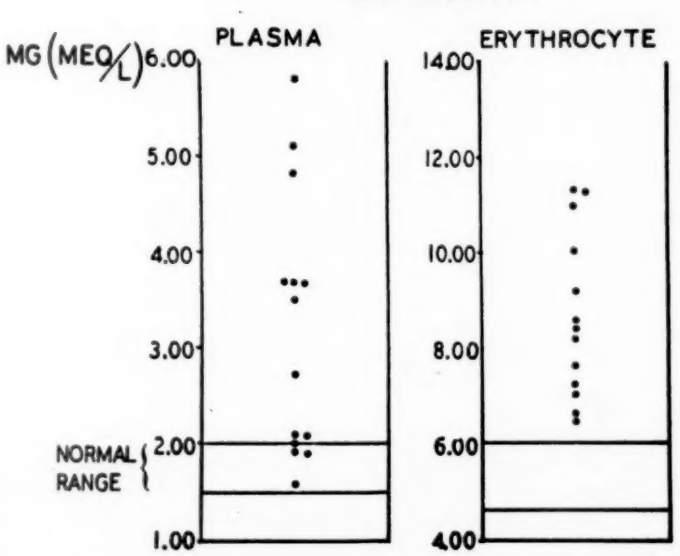

Fig. 2.—Erythrocyte and plasma magnesium values in patients with uremia and CNS depression.

erythrocyte magnesium had risen to 5.19 ± 1.47 mEq. per L. and the mean plasma magnesium to 2.20 ± 0.40 mEq. per L.

UREMIA. Fourteen patients with uremia and central nervous system depression were studied. The mean erythrocyte magnesium concentration was 8.84 ±1.71 mEq. per L. (table). The mean plasma magnesium was 3.17 ± 1.30 mEq. per L. Individual values are again of considerable interest. Four of this group of patients had plasma normal after magnesium therapy. Electrocardiograms were made on 9 of the uremic patients. Abnormalities consisting of depression of the conduction system (atrioventricular block, intraventricular block and prolonged Q–T interval) were found in 6 of them, 2 of whom had no electrolyte abnormality other than the elevated magnesium levels.

ELECTROENCEPHALOGRAMS. An electroencephalogram was made on one of the patients with delirium tremens,

which showed a diffuse dysrhythmia with generalized, fast activity. An encephalogram was made on one of the uremic patients, which showed generalized slowing of activity.

Discussion. McCollister, Flink, and Doe[7] have demonstrated total body depletion of magnesium in alcoholics by metabolic balance techniques. Their data suggest that the deficiency in such cases is much greater than could be accounted for on the basis of extracellular losses only, suggesting a deficiency either in bone or soft tissue stores. these studies, as well as in the present study, a delay in improvement of 12 to 24 hours has been noted invariably. This delay may be on the basis of a rather slow repletion of intracellular stores. It has also been shown that Mg^{++} is separated from the sulfate radicle with considerable difficulty in contrast to the chloride radicle (Walser and Browder[13]), which may contribute to the delayed response. Magnesium chloride would probably be preferable in treating the magnesium deficiency syndrome.

TABLE 1.—STATISTICAL ANALYSIS OF ERYTHROCYTE AND PLASMA MAGNESIUM IN DELIRIUM TREMENS AND UREMIA

	Plasma	*Erythrocyte*
	(*mEq./L.*)	
Healthy Adults		
Mean ± S. D.	1.80 ± 0.13	5.29 ± 0.34
2 S. D. Range	1.54 — 2.06	4.61 — 5.97
Delirium Tremens		
Mean ± S. D.	1.50 ± 0.28	3.19 ± 0.75
P	< .001	< .001
Uremia		
Mean ± S. D.	3.17 ± 1.30	8.84 ± 1.71
P	< .001	< .001

The present study affords evidence that at least one soft tissue cell, the erythrocyte, shows a loss of magnesium in alcoholics with delirium tremens. Whether other body tissues share in this deficiency is only conjectural at this time. The close correlation between the hyperexcitability of the central nervous system with the lowered erythrocyte magnesium levels suggests that the brain cells may also be deficient in magnesium.

Flink[2] has compared the rapidity of improvement in patients with delirium tremens treated by intramuscular magnesium sulfate with such patients not receiving magnesium therapy except in their diet and has found much faster improvement in the treated group. In

The serum or plasma magnesium is a more reliable guide to a total body excess than to a total body deficiency. In a previous study[8] all of the patients with uremia and central nervous system depression had abnormally high values. Hamburger has reported similar results[4]. However, 4 of 14 such patients in the present study had plasma values within the normal range but markedly elevated erythrocyte values.

Summary. Erythrocyte magnesium concentrations have been measured in healthy adults, patients with delirium tremens and uremic patients with central nervous system depression.

The erythrocyte magnesium concentration was abnormally low in all patients with delirium tremens, whereas

the plasma magnesium was abnormally low in only 58% of them.

The erythrocyte magnesium concentration was abnormally high in all patients with uremia and central nervous system depression, whereas 71% had elevated plasma values.

Intracellular fluid magnesium levels, as reflected by the erythrocyte, correlate better with clinical symptomatology than do extracellular fluid (serum) levels, particularly in the magnesium deficiency state.

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SUMMARIO IN INTERLINGUA

Magnesium Intracellular In Delirium Tremens E In Uremia

Le concentration de magnesium in le erythrocytos esseva mesurate in adultos normal, in patientes con delirium tremens, e in patientes uremic con depression del systema nervose central.

Le concentration del magnesium in le erythrocytos esseva anormalmente basse in omne le patientes con delirium tremens, durante que le magnesium del plasma esseva anormalmente basse in solmente 58% de illes.

Le concentration de magnesium in le erythrocytos esseva anormalmente alte in omne patientes con uremia e depression del systema nervose central, durante que le magnesium del plasma esseva elevate in 71% de illes.

Le nivellos del magnesium in fluido intracellular (reflectite per le erythrocytos) se correlationa melio con le symptomatologia clinic que le nivellos del magnesium in fluido extracellular (sero), specialmente in statos de carentia de magnesium.

LIPID MOBILIZATION AS A CONSEQUENCE OF SURGICAL STRESS

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A lipid mobilizing hormone (LM) was discovered in the plasma of man and other species by Seifter and Baeder[5] in 1954. These workers later isolated LM from the posterior pituitary gland of hogs[6], and further demonstrated that the plasma content of LM is greatly increased by the administration of cortisone or by subjecting animals to various stresses, including starvation[7,8]. Dialyzates and crystalline material prepared from the plasma of cortisone-treated horses have been used to determine the effect of LM administration in man. It was observed that the intravenous injection of LM into fasting patients was followed by a prompt and striking increase in the plasma cholesterol, fatty acids, and lipid phosphorus (Steiger *et al.*[11], Zarafonetis *et al.*[14,16]). When LM was administered daily to subjects maintained on a diet containing very little fat, a sustained hyperlipemia was induced. On the other hand, nonfasting subjects and patients on a high fat diet did not show a response to intravenous injections of LM (Zarafonetis *et al.*[15]). These and other observations led to additional studies which demonstrated that prefeeding with glucose or cream, but not with amino acids, would block the hyperlipemic response to intravenously administered LM (Zarafonetis *et al.*[16]). In this connection, Seifter and Baeder found that injections of LM into animals were uniformly followed by mobilization of triglycerides from the mesenteric depots[8,10]. Whether or not an animal so treated exhibited hyperlipemia of the peripheral blood depended on the capability of its liver to handle the lipids presented to it. Furthermore, certain factors which influenced the ability of the liver to metabolize the mobilized lipids were determined. Adequate stores of glycogen would permit the liver to retain and metabolize LM-mobilized triglycerides, whereas severe depletion of glycogen modified liver lipid metabolism with resultant peripheral hyperlipemia. It thereby became evident that, in animals, the liver played a key role in the manifest response to intravenous injections of LM, or to endogenous LM released under situations of stress.

A series of investigations were undertaken, therefore, to determine whether the observations made in experimental

animals were applicable to man under conditions of acute stress. Preliminary observations (Zarafonetis *et al.*[17]) indicated that man did respond to the stress of an operative procedure with the release of endogenous LM. The present report deals with an extension of these studies to a large series of subjects in whom the effect of surgical stress on the prehepatic and peripherally circulating plasma lipids was studied. In addition, these findings will be correlated with the concentrations of endogenous plasma LM as determined by *in vitro* and *in vivo* assay. Finally, attention will be drawn to the finding of marked changes in the prehepatic lipoprotein pattern during periods of surgical stress.

Materials and Methods. Observations were made on 26 individuals during the course of various operative procedures at the Temple University Hospital (Tables 1 and 2). One of the patients (B.M.) was followed through right cervical sympathectomy, and one week later through what amounted to a "sham" operation. It had been planned to perform a sym-

TABLE 1.—GROUP I PATIENTS FROM WHOM ONLY ANTECUBITAL VEIN BLOOD SAMPLES WERE OBTAINED BEFORE AND 4 HOURS AFTER INDICATED SURGICAL PROCEDURE.

No.	*Patient*	*Age*	*Sex*	*Operation*
1	G. L.	18	M	Splenectomy (idiopathic thrombocytopenic purpura)
2	T. H.	56	F	Transurethral resection of bladder tumor
3	N. W.	65	F	Laparotomy, excision of cystic duct
4	B. H.	26	F	Cholecystectomy (typhoid carrier)
5	M. R.	23	F	Right cervical sympathectomy (collagen disease)
6	C. C.	26	M	Exploratory laparotomy
7	A. M.	29	F	Splenectomy (idiopathic thrombocytopenic purpura)
8	S. T.	55	F	Cholecystectomy
9	E. N.	25	F	Splenectomy (idiopathic thrombocytopenic purpura)
10	T. L.	47	F	Oophorectomy (bilateral)
11	G. T.	55	M	Peet sympathectomy (bilateral)
12	J. S.	42	M	Cholecystectomy
13	B. G.	49	F	Exploratory laparotomy, liver biopsy
14	G. G.	38	M	Internal mammary ligation
15*a.*	B. M.	29	M	Rt. cervical sympathectomy (collagen disease)
b.	B. M.	29	M	"Sham"*

*While the patient was on the operating table, anesthetized and prepared for left cervical sympathectomy, the right sympathectomy wound opened revealing infection surrounded by poor granulation tissue. Therefore, no operation was done at this time.

TABLE 2.—GROUP II PATIENTS FROM WHOM OMENTAL ARTERY AND VEIN AS WELL AS ANTECUBITAL VEIN BLOOD SAMPLES WERE OBTAINED.

No.	*Patient*	*Age*	*Sex*	*Operation*
1	F. H.	26	F	Cholecystectomy,appendectomy, repair umbilical hernia
2	W. G.	68	M	Exploratory laparotomy, gastrotomy
3	K. R.	74	F	Proctosigmoidectomy
4	R. R.	42	M	Subtotal gastrectomy
5	A. A.	69	F	Cholecystectomy
6	A. S.	41	F	Gastrectomy
7	S. G.	15	F	Splenectomy (idiopathic thrombocytopenic purpura)
8	H. T.	55	F	Panhysterectomy
9	E. T.	34	F	Cholecystectomy
10	M. M.	57	F	Cholecystectomy
11	B. L.*	30	F	Excision pancreatic cyst

*Following collection of the initial omental blood specimens, an intravenous injection of LM, 5 mg. per kg. of body weight, was given to this patient. After a 20-minute interval during which there was no manipulation of the abdominal organs, the post-injection blood specimens were drawn, and then the operative procedure was resumed.

pathectomy of the left cervical region, and the patient was prepared and anesthetized accordingly. However, as he was turned on the operating table, the wound of the right sympathectomy opened, revealing infection surrounded by poor granulation tissue. Therefore, no operation was done at this time.

Complete history, physical examination, and conventional or special laboratory tests were performed in each case. In addition, record was made of all recent or concurrent chemotherapy or antibiotic administration, of the pre-operative medications, anesthetics, and parenteral fluid or blood administration during the course of operation and the postoperative period. All of the patients were fasted overnight and throughout the day of operation, or at least until the postsurgery blood sampling had been completed. Glucose was omitted from the parenteral fluids administered to these patients during the test period.

For convenience, the patients have been placed in 2 groups: Group I (Table 1) includes those individuals from whom only antecubital vein blood was drawn for testing. In these cases, specimens of antecubital vein blood were obtained before and 4 hours after completion of the operation. In Group II cases (Table 2), similar antecubital vein specimens were obtained, but, in addition, blood samples were taken from branches of the omental artery and omental vein at the beginning and at the end of the intra-abdominal operative procedure.

All of the blood specimens were analyzed for cholesterol (Schoenheimer and Sperry[4]) and total fatty acids (Stoddard and Drury[12]), and were assayed for lipid mobilizer hormone activity as described below.

LIPID MOBILIZER HORMONE ASSAYS. Tests for LM hormone activity were carried out both *in vitro* and *in vivo*. Briefly, the *in vitro* method makes use of the ability of LM to inhibit the delactescing action of heparin clearing factor. Normal human plasma will not prevent heparin clearing factor activity, whereas plasmas containing increased amounts of LM will delay or completely block this clearing mechanism (Fig. 4*a* and *b*).

The *in vivo* tests for LM activity were performed initially as follows: The plasma to be tested was dialyzed through viscose No-jax casing in a volume of sterile deionized water that was 4 times greater than that of the plasma. After 24 hours of dialysis, the dialyzate was freeze-dried for 18 hours, after which it was injected intravenously at doses of 1.0, 5.0, and 10.0 mg. per kg. into fasted, sensitized rats. The rats were sacrificed 2 hours later and lipid analyses were made on blood samples obtained from the heart. Animals which received dialyzates of normal plasma showed no elevation of their blood lipids, whereas dialyzates of plasma containing increased amounts of LM gave rise to significant (50% or more) elevations in the plasma lipids of the test rats.

While this study was underway, a second, simpler form of *in vivo* LM assay was devised by Baeder and Seifter[2] and was applied to the bulk of the specimens tested. It is performed in the anesthetized rat in which the gastro-epiploic vein is exposed, and a fine siliconized catheter inserted through it to the portal vein. Closure is made with the catheter exteriorized. Baseline portal vein blood is withdrawn, and 0.25 ml. of test plasma is injected into a recurrent saphenous vein. Additional portal vein samples are taken at 20 minutes and 40 minutes, and these along with the baseline specimen are analyzed for total fatty acids by the method of Stoddard and Drury[12]. Appropriate controls are run with each series of tests (Table 5). The method is reliable and relatively rapid.

LIPOPROTEIN PATTERNS. All of the plasma specimens from several of the Group II patients were subjected to paper electrophoretic analysis for their lipoprotein patterns. The separation was carried out in a flat bed electrophoresis apparatus with ice water cooled chambers for the paper. Electrophoresis was run on Whatman 3 MM paper strips in barbital buffer, pH 8.6, ionic strength 0.5 at 17 milliamps., 750 volts for 2 hours. The strips were then stained in Oil Red O for 18 hours, washed with distilled water, dried in a current of warm air, and read in a Photovolt densitometer.

Results. The results of the cholesterol and fatty acid determinations on the plasma lipids and LM assays of the Group I patients are given in Table 3 and those of the Group II patients in Tables 4*a*, *b*, and *c*. Results in 2 individual cases are presented in Fig. 1*a* and *b*, and Fig. 2*a* and *b*. These may be compared to the findings in patient B.L. who was given an injection of LM after the baseline omental blood samples had been obtained (Fig. 3*a* and *b*).

1. EFFECT OF STRESS OF SURGICAL PROCEDURE ON PLASMA LM CONTENT. With few exceptions, the assays for LM were

negative in tests on the pre-operation antecubital vein blood specimens, and on the omental arterial and venous blood samples taken at the beginning of intra-abdominal operations. Patients 1, 5, and 9 in Group I, who gave evidence of increased plasma LM content in the baseline specimens, were under corticosteroid therapy for their respective diseases, while patient 14 was under severe dietary restriction for the treatment of his familial hypercholesterolemia. One Group II patient (Case 2, Table 4*a*) had a slight increase in the plasma LM assay of his baseline blood specimen. All of the subjects in both groups exhibited an increase in plasma LM in the late surgery and postoperation blood samples (Tables 3 and 4*a*).

Representative results of LM assays by the *in vitro* inhibition of heparin-activated lipemia-clearing activity are shown in Fig. 4*a* and *b*, while an example of the bio-assay test findings is given in Table 5, in which it may be noted that the pre-operation and early operation plasma specimens from the patient induced no rise in the portal vein fatty acids of the test rats. Late operation and postoperation plasma specimens, on the other hand, produced increases in portal vein fatty acids similar in timing and extent to that resulting from the injection of 5 mg. of LM per kg. of body weight into a control animal.

TABLE 3.—CHOLESTEROL AND FATTY ACID DETERMINATIONS, AND LIPID MOBILIZER ASSAYS IN GROUP I PATIENTS.

	Baseline			*4 Hours Postop.*			*% increase from baseline value*	
Case No.	*Chol. mg./100 ml.*	*Fatty Acids mg./100 ml.*	*LM Assay*	*Chol. mg./100 ml.*	*Fatty Acids mg./100 ml.*	*LM Assay*	*Chol.*	*Fatty Acids*
1	472	535	Pos.	866	1072	Pos.	83.4	100.0
2	226	239	Neg.	265	302	Pos.	17.2	26.4
3	201	227	Neg.	248	290	Pos.	23.2	27.7
4	217	240	Neg.	232	256	Pos.	7.0	6.6
5	224	286	±	324	418	Pos.	44.7	46.1
6	302	378	Neg.	337	412	Pos.	11.5	8.9
7	326	384	Neg.	378	496	Pos.	15.9	29.1
8	216	312	Neg.	302	335	Pos.	39.9	7.3
9	290	313	±	344	386	Pos.	18.6	23.6
10	202	212	Neg.	308	356	Pos.	52.4	67.9
11	254	286	Neg.	292	312	Pos.	18.9	9.1
12	284	307	Neg.	357	392	Pos.	25.7	27.7
13	237	209	Neg.	242	310	±	2.1	48.3
14	272	311	Pos.	286	324	Pos.	37.2	57.1
15*a.*	298	396	Neg.	308	454	Pos.	5.1	4.1
*b.**	232	254	Neg.	320	399	Pos.	3.3	14.1
						Avg.	25.4%	31.5%

*See legend to Table 1.

2. EFFECTS OF STRESS OF SURGICAL PROCEDURE ON PLASMA LIPIDS. a. *Antecubital vein blood.* It can be seen from inspection of Table 3 that the postoperative plasma cholesterol values of the Group I patients increased an average of 25.4% (range 2.1 to 83.4%) over the baseline pre-operative values, while the rise in total fatty acids averaged 31.5% (range 4.1 to 100%). For the comparable antecubital vein samples in the Group II patients, the cholesterol rose an average of 26.3% (range −2.6% to +62.1%), and the fatty acids increased 41.5% (range 5.2 to 194.3%).

TABLE 4*a*.—RESULTS OF CHOLESTEROL AND FATTY ACID DETERMINATIONS AND LIPID MOBILIZER ASSAYS IN GROUP II PATIENTS

Time + Site of Blood Samples		*Determination*	*Case No.* 1	2	3	4	5	6	7	8	9	10	11*
Pre-operative baseline	Antecubital vein	Cholesterol mg./100 ml.	190	290	222	146	190	274	312	214	238	208	317
		Fatty Acids mg./100 ml.	212	374	238	284	212	314	328	286	290	296	382
		LM Assay	Neg.	±	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Beginning of operation	Omental Artery	Cholesterol mg./100 ml.	186	272	238	254	186	294	312	226	228	232	312
		Fatty Acids mg./100 ml.	214	306	252	274	214	212	348	312	280	338	356
		LM Assay	Neg.		Neg.	Neg.	Neg.		Neg.	Neg.	Neg.	Neg.	Neg.
	Omental Vein	Cholesterol mg./100 ml.	154	202	202	228	142	230	303	202	212	201	308
		Fatty Acids mg./100 ml.	218	298	208	286	208	138	326	314	254	312	352
		LM Assay	Neg.		Neg.	Neg.	Neg.		Neg.	Neg.	Neg.	Neg.	Neg.
Time elapsed to next omental samples			2½ hr.	1½ hr.	3½ hr.	2 hr.	2 hr.	1¾ hr.	2 hr.	2 hr.	1½ hr.	1½ hr.	20 min.
End of operation	Omental Artery	Cholesterol mg./100 ml.	196	292	290	251	196	284	346		280	248	330
		Fatty Acids mg./100 ml.	232	312	326	290	394	312	402		308	360	360
		LM Assay	Pos.		Pos.	Pos.	Pos.		Pos.		Pos.	Pos.	±
	Omental Vein	Cholesterol mg./100 ml.	184	213	284	220	188	227	338	226	202	209	328
		Fatty Acids mg./100 ml.	386	417	852	446	786	506	648	413	499	440	524
		LM Assay	Pos.		Pos.	Pos.	Pos.		Pos.	Pos.	Pos.	Pos.	±
4 hours Postoperative	Antecubital Vein	Cholesterol mg./100 ml.	185	297	299	296	308	340	352	344	295		396
		Fatty Acids mg./100 ml.	246	399	372	342	624	398	412	408	352		402
		LM Assay	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.		±

*See legend to Table 2

TABLE 4*b*.—PERCENTAGE CHANGES* IN PLASMA CHOLESTEROL AND FATTY ACID VALUES OF GROUP II PATIENTS.

Case No.	*Antecubital Vein*		*Omental Artery*		*Omental Vein*	
	Chol.	*Fatty Acids*	*Chol.*	*Fatty Acids*	*Chol.*	*Fatty Acids*
1	— 2.6%	+16.0%	+ 5.3%	+ 8.4%	+19.5%	+77.1%
2	+ 2.4	6.7	7.3	1.9	5.4	39.9
3	+34.7	56.3	21.8	29.3	40.6	309.6
4	+20.3	20.4	— 1.2	5.9	— 3.5	55.9
5	+62.1	194.3	5.3	84.1	20.1	277.9
6	+24.1	26.7	— 3.4	47.1	— 1.3	266.6
7	+12.8	25.6	10.9	15.5	11.5	98.8
8	+60.7	42.6	—	—	11.8	31.5
9	+23.9	21.4	22.8	10.0	— 4.7	96.5
10	—	—	6.9	6.5	3.9	44.2
11	+24.9	5.2	5.8	1.1	6.5	48.9
Avg.	+26.3%	+41.5%	+ 8.1%	+ 20.9%	+ 10.9%	+ 122%

*Calculated from data in Table 4*a*.

TABLE 4*c*.—ARTERIOVENOUS DIFFERENCES* IN PLASMA CHOLESTEROL AND FATTY ACID VALUES AT BEGINNING AND END OF INTRA-ABDOMINAL PROCEDURES (GROUP II PATIENTS.)

Case	*Cholesterol—difference in mg./100 ml.*		*Fatty Acids—difference in mg./100 ml.*	
	Begin. Oper.	*End Oper.*	*Begin. Oper.*	*End Oper.*
1	—32	—12	+ 4	+154
2	—70	—79	— 8	+105
3	—36	— 6	—44	+526
4	—26	—31	+12	+156
5	—44	— 8	— 6	+392
6	—64	—57	—74	+194
7	— 9	— 8	—22	+246
8	—24	—	+ 2	—
9	—16	—78	—26	+191
10	—31	—39	—26	+ 80
11	— 4	— 2	— 4	+164
Avg.	—32	—32	—19.2	+220.9

*Differences between omental artery and omental vein values calculated from data in Table 4*a*.

b. *Omental artery blood.* The changes which occurred in the plasma cholesterol and fatty acids of the omental arterial blood specimens are shown in Tables 4*a*, *b*, and *c*. Although there was a slight decrease in 2 instances, the remaining subjects had increases with the resultant average rise of 8.1% in the cholesterol values and 20.9% in the fatty acids (range 1.1 to 84.1%).

c. *Omental vein blood.* From inspection of the results given in Table 4*b*, it is evident that the changes in cholesterol were of about the same order (avg. +10.9%) on the venous side of the omental circulation as were noted for the arterial samples. The concentration of fatty acids, however, showed a marked increase which averaged 122% over the baseline values, with a range of from +31.5 to +309.6%.

d. *Arteriovenous differences of cholesterol values.* In Table 4*c* are indicated the differences between the omental artery and omental vein cholesterol values at the beginning and at the end of the intra-abdominal surgical

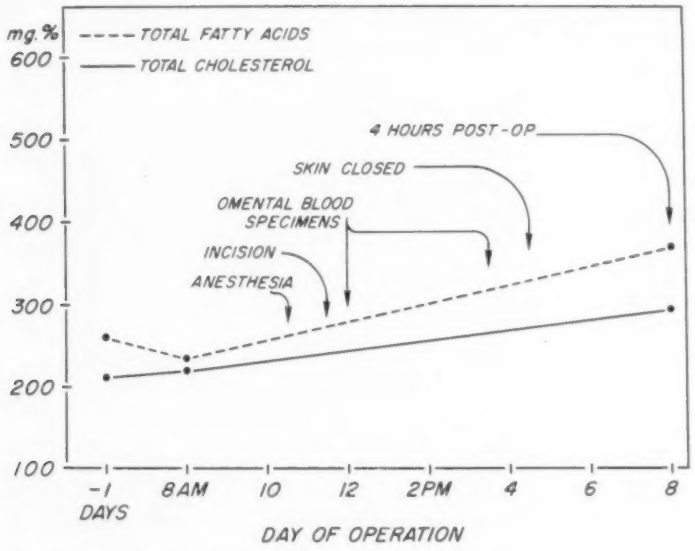

Fig. 1*a*.—Plasma lipid values (antecubital vein blood) of patient K.R., a 74-year-old white woman, before and after sigmoidectomy. Note relatively small postoperation increase of peripheral lipid values despite sharp rise in omental vein fatty acids as shown in Fig. 1*b*.

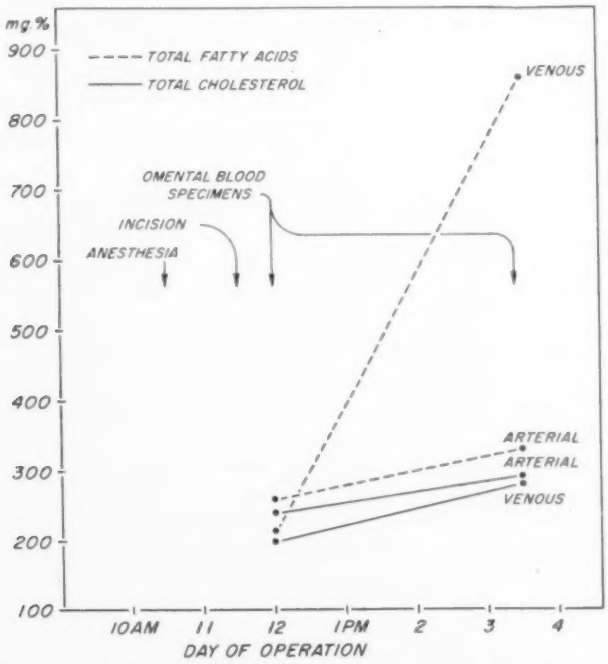

Fig. 1*b*.—Plasma lipid values of omental artery and omental vein blood specimens taken at indicated times from patient, K.R., during sigmoidectomy. Note marked increase of fatty acids in pre-hepatic blood obtained from omental vein late in surgery over levels found in the baseline specimens and in omental arterial blood taken at the same time.

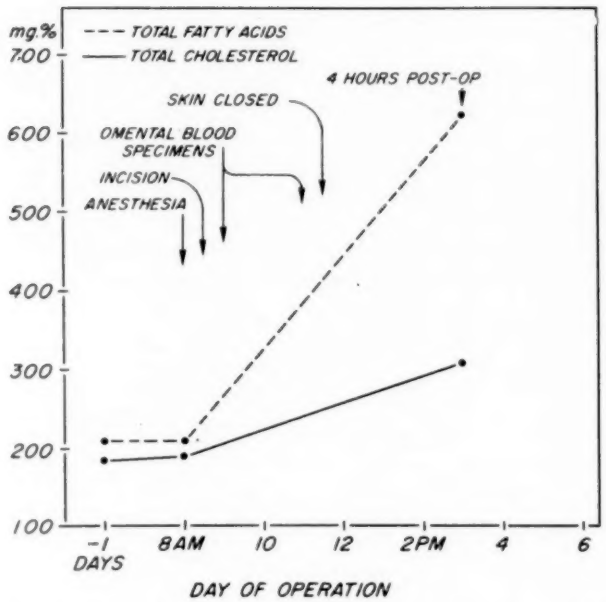

Fig. 2*a*.—Plasma lipid values (antecubital vein blood) of A.A., a 69-year-old Negro woman, before and after cholecystectomy. In contrast to case shown in Fig. 1*a*, there is a marked rise in the fatty acids of the peripheral blood drawn 4 hours after operation.

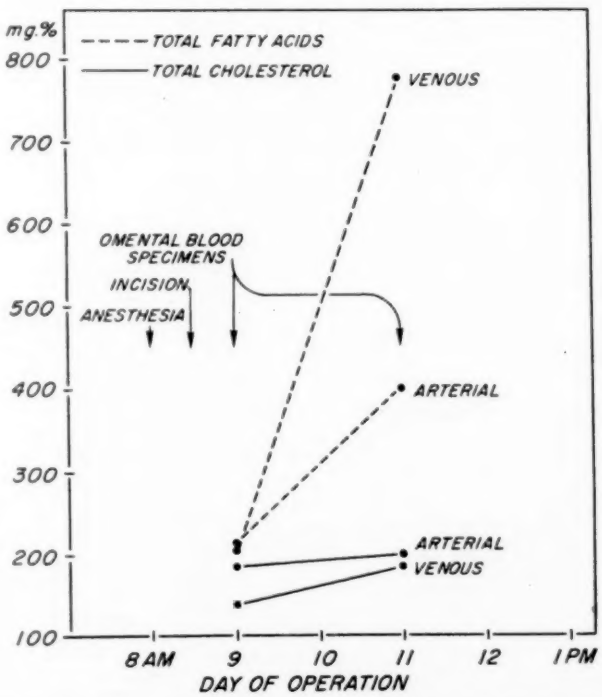

Fig. 2*b*.—The plasma lipid values of the indicated omental blood specimens are shown for patient A.A. It may be seen that there is a marked increase in pre-hepatic fatty acids. However that the patient's liver has only partially removed the fatty acids presented to it is inferred from the evident increase in fatty acids on the arterial side as well.

procedures. In every case, the cholesterol value was somewhat lower on the venous than on the arterial side. The average difference was −32 mg. per 100 ml., both at the beginning and at the end of the operations.

e. *Arteriovenous differences of fatty acid values* (Table 4*c*). At the beginning of the operation, the average value for fatty acids was 19.2 mg. per 100 ml. less in the venous specimens than was found in the arterial plasmas. At the end of the operations, however, there was a marked increase in the plasma fatty acids of the omental vein bloods over that present in the arte-

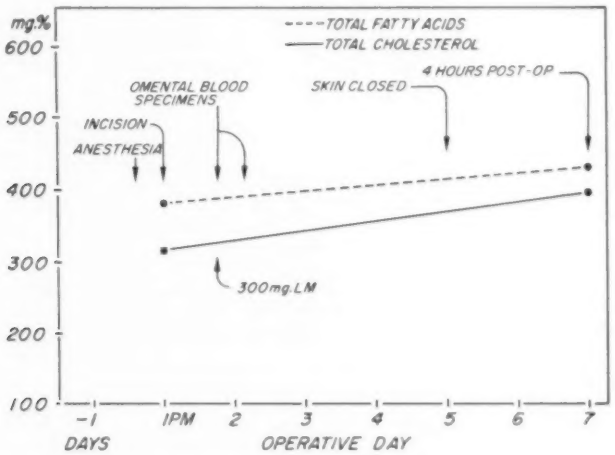

Fig. 3*a*.—Plasma lipid values (antecubital vein blood) of patient, B.L., before and after injection of lipid mobilizer hormone dialyzate and excision of pancreatic cyst.

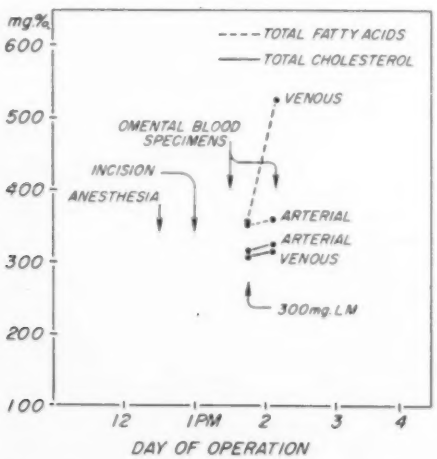

Fig. 3*b*.—Plasma lipid values of omental artery and vein blood specimens taken from patient, B.L., before and 20 minutes after intravenous injection of 300 mg. of lipid mobilizer hormone dialyzate. Note sharp rise of omental vein fatty acids following administration of LM.

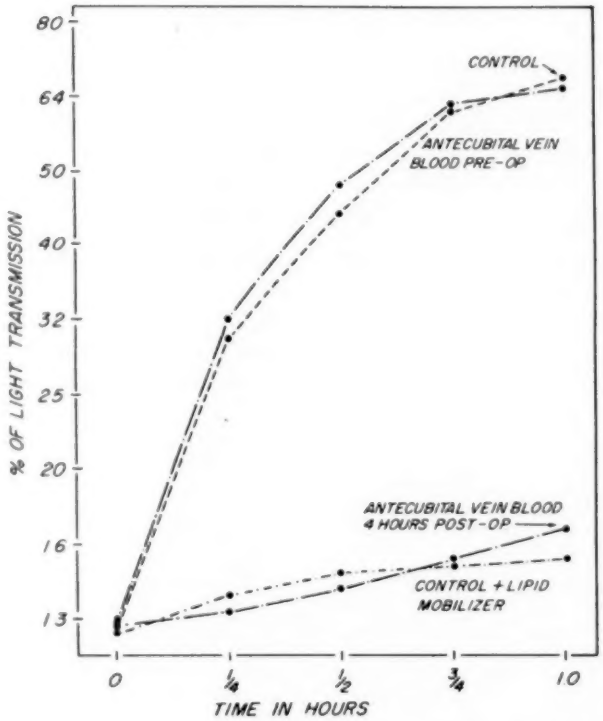

Fig. 4*a*.—Results of *in vitro* assays of LM in plasma specimens obtained from patient, A.A., before and after cholecystectomy. (See also Fig. 2*a*.) Note that postoperation plasma inhibited *in vitro* clearing in test system, whereas pre-operation plasma did not. Lipid mobilizer added to the test system also inhibited the heparin activated clearing mechanism.

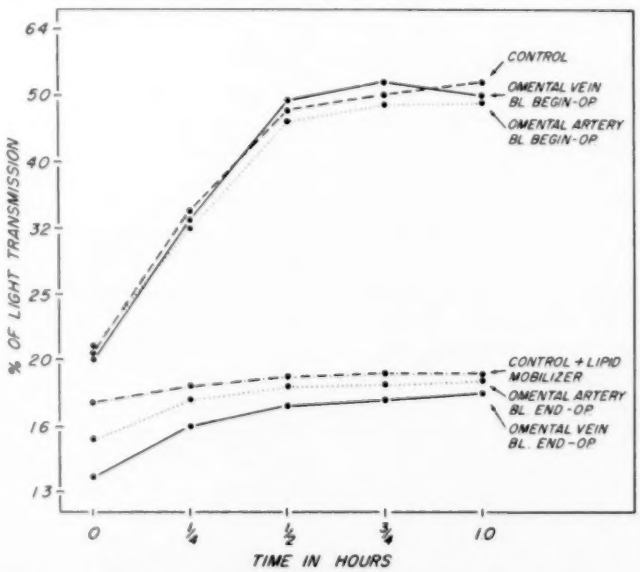

Fig. 4*b*.—Results of *in vitro* assays of LM on the omental artery and vein blood specimens obtained from patient, A.A. (See Fig. 2*b* and 4*a*). Note that the specimens obtained late in the course of surgery exhibited inhibition of clearing, while the early specimens did not.

rial specimens. The increase ranged from +80 mg. to + 526 mg., and averaged + 220.9 mg. per 100 ml.

3. EFFECT OF STRESS OF SURGICAL PROCEDURE ON THE ELECTROPHORETIC PATTERN OF PLASMA LIPOPROTEINS. Paper electrophoretic analysis of the lipoproteins was performed on representative series of plasma specimens from these patients. In each case, there was a striking shift from α-lipoprotein to β-lipoprotein predominance in the electrophoretic patterns of omental vein blood during the course of surgery.* This occurred in the absence of significant changes in the patterns obtained on specimens taken at the same time from the omental artery, or in the pre- and postoperative antecubital vein samples. This type of finding is illustrated in Fig. 5*a*, *b*, and *c*. In other cases, there was evidence of a "spilling over" of the mobilized β-lipoproteins presented to the liver, with resultant increase in the β-lipoproteins of plasma specimens obtained postoperatively from the antecubital vein. An example of this finding is shown in Fig. 6*a*, *b*, and *c*.

TABLE 5.—BIOASSAY RESULTS OF LM HORMONE ACTIVITY AND PLASMA LIPID VALUES OF A. A., 69-YEAR-OLD NEGRO WOMAN, BEFORE, DURING, AND AFTER CHOLECYSTECTOMY.

	Portal vein fatty acids (rat) after injection of patient's plasma			*Lipid values—patient's plasma*	
Plasma from patient:	*Baseline mg./100 ml.*	*20 min. mg./100 ml.*	*40 min. mg./100 ml.*	*Fatty acids mg./100 ml.*	*Cholesterol mg./100 ml.*
Antecubital vein (fasting)	108	102	106	207	184
Antecubital vein (preop.)	108	106	106	212	190
Omental artery (begin. op.)	102	104	104	214	186
Omental vein (begin. op.)	106	108	110	208	142
Omental artery (end op.)	110	148	162	394	196
Omental vein (end op.)	102	158	174	786	188
Antecubital vein (4 hrs. postop.)	104	152	170	624	308
LM control—5 mg./kg.	102	158	174		

Discussion. The foregoing results indicate that several dynamic events referable to lipid metabolism may occur in patients subjected to the stress of surgery. Under the conditions of study, the over-all stresses which are inherent in operations led to the release of endogenous lipid mobilizer hormone during the course of surgery. This is inferred from the finding that all of the assays were positive for increased amounts of LM in tests on blood samples drawn late in the operation or postoperatively. LM assays on preoperation and early operation blood specimens, however, were negative with 5 exceptions. Of these, 3 were patients receiving cortisone for the treatment of their respective diseases, while a fourth was a patient on dietary restriction for familial hypercholesterolemia. Since the administration of cortisone has been shown to increase plasma LM (Seifter and Baeder[7,8], Seifter *et al.*[10]), it would appear reasonable to conclude that this was the basis for the positive LM assays found in the baseline blood specimens from the 3 patients so treated. The finding of increased amounts of LM in the patient with familial hypercholesterolemia is in keeping with our observations that subjects with this

*Dr. Harvey W. Watts, Department of Pathology, Temple University School of Medicine, obtained similar patterns on plasma specimens from patients in this series.

Fig. 5.—Paper electrophoretic patterns of plasma lipoproteins in blood samples obtained from patient, B.L. (See Fig. 3). As can be seen, there was no significant change in the lipoproteins of the omental artery specimens (5*a*) or of the peripheral (antecubital vein) specimens (5*c*); on the other hand, there was a striking shift from α-lipoprotein to β-lipoprotein predominance in the omental vein blood within 20 minutes after the administration of LM (5*b*).

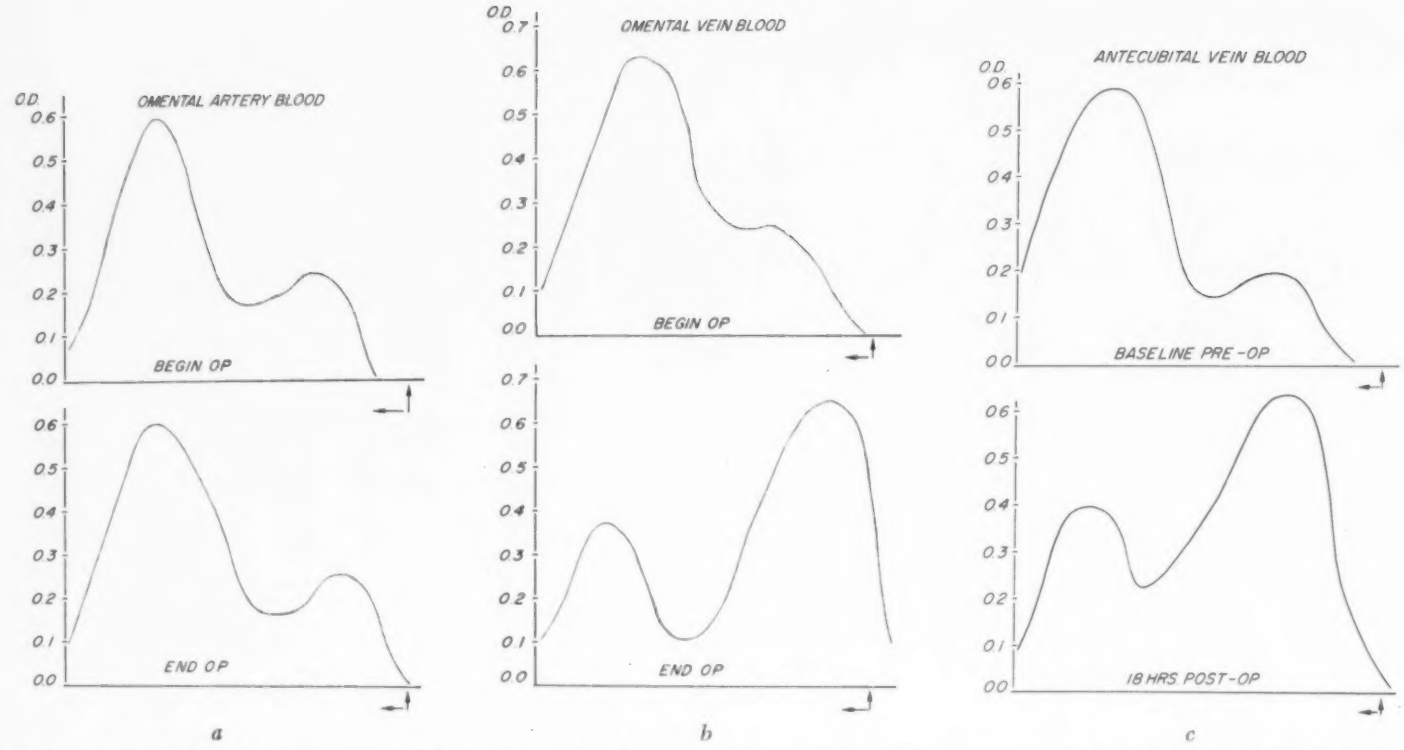

Fig. 6.—Paper electrophoretic patterns of plasma lipoproteins of patient, M.M., a 57-year-old Negro woman, before, during, and after cholecystectomy. Note that while there is no significant difference in the specimens from the omental artery (5*a*), a marked alteration to β-lipoprotein predominence occurred in the late omental vein (5*b*) and antecubital vein (5*c*) specimens.

disorder have chronically elevated amounts of plasma LM[17]. If these 4 patients are excluded, there remains only one instance in which there was evidence of some increase in the plasma LM content prior to surgery. With this possible exception, it would appear that any anxiety which may have been felt by these subjects before operation was not a sufficiently stressful stimulus to cause a pre-operative increase in plasma LM. This is of particular interest in view of recent investigations which point to a relationship between blood lipids and emotional stresses. It is presumed that any concern our patients may have held for their operative results was not sustained over sufficiently long periods to be comparable to the emotional and mental stresses implicated in this connection by others (Rosenman and Friedman[3], Wertlake *et al.*[13]).

With regard to the plasma lipids, it was found that a number of important changes were exhibited during the course of surgery. These changes, it is noted, coincided with, and were apparently the result of, the above indicated rise in plasma LM content. Tests on antecubital vein samples, which were taken 4 hours after operation, showed an average increase of 26% in the cholesterol and 41% in the fatty acid values over the baseline specimens. An even more impressive rise in fatty acids was found in the omental vein samples taken late in the course of intra-abdominal procedures. From Table 4*b*, it can be seen that this increase in fatty acids averaged 122% over the baseline values. Cholesterol, however, increased only about 11% during the same period. The lipid changes in the omental arterial blood were intermediate between those noted in the specimens obtained from the antecubital vein and those taken from the omental vein. The reasons for these differences in plasma lipid values on the blood specimens taken from different sites are twofold. First, the timing of the omental specimens was necessarily intermediate between that for baseline and postoperation peripheral blood (antecubital vein) specimens. Secondly, it should be evident from the data in Tables 4*a*, *b*, and *c* that two areas contributed significantly to the development of differences in the plasma lipids, namely, the omentum and the liver. Thus, it was found that cholesterol was removed from the circulation during passage of the blood through the omentum. This held true both at the beginning and at the end of the intra-abdominal phase of operation. On the other hand, while some removal of fatty acids appeared to take place during circulation of the blood through the omentum at the beginning of such operations, there was a remarkable increase of plasma fatty acids in the venous (pre-hepatic) blood by the end of the procedures. This increase averaged 221 mg. per 100 ml. in the 11 cases so studied (Table 4*c*).

In addition to chemical lipid analyses, determinations of the plasma lipoprotein patterns were made by paper electrophoresis on representative blood specimens from these patients. There was detected a striking shift in the lipoprotein pattern of omental vein blood drawn at the end of the operation as compared with the findings at the beginning of the abdominal procedure. This change in pattern was characterized by a marked increase in the β-lipoprotein component of the curve (Figs. 5 and 6).

Therefore, increased triglycerides and alteration of lipoprotein patterns as determined by paper electrophoresis were contributed by the omentum to the pre-hepatic circulation, while at the same time some cholesterol was removed from the blood passing through

it. With these points in mind, the role of the liver in modifying the circulating plasma lipids of these patients will be considered. For the purpose of simplification, the antecubital vein specimens and the omental artery blood specimens may be regarded as post-hepatic samples. From the data shown in Tables 3 and 4*a*, *b*, and *c*, it is evident that a rise in the average of the cholesterol values occurred in these post-hepatic specimens during the course of surgery. Although not shown in the data, similar increases in lipid phosphorus values were observed in tests on these same blood samples. Studies in intact and in hepatectomized animals (Baeder and Seifter[1], Seifter and Baeder[6,9]) further support the inference drawn from these data, that is, that the observed increase in plasma cholesterol (and lipid phosphorus) was contributed by the liver of the respective patients. In this connection, Seifter and Baeder[6] conclusively demonstrated that the liver was the source of cholesterol and lipid phosphorus in rats made hyperlipemic by the injection of LM.

It should be clear, therefore, that the changes which appear in the peripheral (post-hepatic) blood after lipid mobilization through the action of LM hormone depend on the manner in which the liver metabolizes the lipid load presented to it. Some patients may exhibit marked increases in fatty acids, cholesterol, and lipid phosphorus and at the same time show a shift in the paper electrophoretic pattern to β-lipoprotein predominance. Others, however, may show no significant changes in the peripheral blood findings even though mobilization of lipids from the omental depot has occurred. Case 2 in Table 4*b*, for example, shows an increase in cholesterol of only 2.4% in the post-surgery specimen over the pre-operation value. The rise in post-hepatic plasma fatty acids was similarly minimal in this patient, even though the pre-hepatic samples indicated a significant (34%) increase in this component.

The possibility needs to be considered that manipulation of the omentum caused the lipid changes in the omental vein blood rather than the action of endogenous LM. In this regard, it should be noted that some patients whose operations entailed little or no trauma to the omentum exhibited greater increases in fatty acids than did others whose operations involved more handling of it. Moreover, the response elicited by the injection of LM into patient B.L. (Fig. 3), without trauma to the omentum, was similar to that observed in the other cases. Finally, in studies which are yet to be reported, it has been found that the mobilization of lipids from the omental depot can be completely prevented by prior administration of a partially depolymerized hyaluronic acid (Seifter *et al.*[10], Zarafonetis *et al.*[18]). Were manipulation of the omentum the basis for the observed increase in the pre-hepatic blood lipids, then it should not have been prevented by such prior medication.

Summary and Conclusions. The effect of surgical stress on the plasma concentration of lipid mobilizer hormone and on the plasma lipids was investigated in 26 patients.

Lipid mobilizer hormone assays, cholesterol and fatty acid determinations, and paper electrophoretic patterns of lipoproteins were made on blood specimens obtained from the antecubital vein before and 4 hours after operation. Similar tests were performed on samples taken from the omental artery and the omental vein at the beginning and at the end of intra-abdominal procedures.

The most important findings and

their implications may be listed as follows:

1) Evidence was obtained that lipid mobilizer hormone is released during surgical stress; 2) this leads to mobilization of triglycerides from the omental depot; 3) there is a marked shift in paper electrophorograms from α-lipoprotein to β-lipoprotein predominance in the omental vein blood during surgery; 4) the omentum not only responds actively to endogenous LM with an outpouring of the aforementioned lipid components, but also appears to remove cholesterol from the blood circulating through it; and 5) the lipid changes which may occur in the peripheral blood during surgical stress reflect the foregoing events as well as the capability of the liver to metabolize the lipids presented to it.

It is concluded that these observations made in patients undergoing the stress of surgery permit the delineation of a physiologic mechanism in man for the acute mobilization of lipids to the liver.

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(Interlingua on page 539)

THE COMPARATIVE VECTORGRAM: A SIMPLE METHOD FOR ANALYSIS OF LEAD SIMILARITY

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The requirement to compare similar potential of identical or opposite polarity arises frequently in the study of electrical fields created by the heart. "Mirror image" electrocardiographic tracings have been used to study "proximity potentials" (Wilson *et al.*[21]) of the human heart and to evaluate the concept that a single fixed resultant dipole reasonably represents the electrical cardiac cycle (Frank[4], Levine, Schmitt and Simonson[13], Milnor, Talbot and Newman[14], Schmitt *et al.*[18,19]).

The existence of mirror image potentials on the surface of the human body can be readily demonstrated. A wave of potential is recorded at one point in respect to a fixed reference point, commonly the Wilson central terminal. By trial and error, a second point is found which has a similar potential wave form when measured against the same fixed reference point. Although the wave forms are similar, they may be of the same or opposite polarity, and usually are of different amplitude. Grant and Estes[5,6] and Langner, Dewees and Moore[11] have illustrated this principle through the use of mosaic maps demonstrating the unipolar potentials recorded at points over the entire thorax.

In attempting to achieve the greatest accuracy in determining how nearly two wave forms represent true mirror patterns, inspection and measurement of electrocardiographic tracings is not altogether satisfactory. Even though simultaneous recordings may be utilized to minimize timing errors, this remains a time consuming method, subject to inaccuracies.

Cancellation techniques have been used by Schmitt and associates[13,18,19] and by Frank[4]. They used the method of electrically summating the unipolar potential recorded at two points and equalizing the maximum potential with "mirror" or center-tapped potentiometers connected between the unipolar leads. The resulting potential ("residual potential") throughout the cardiac cycle was recorded. The smaller the residual potential after equalizing the two maximum potentials, the greater is the accuracy of cancellation or mirror image characteristics.

Swiss investigators (Grosgurin and Duchosal[7], Hartmann, Veyrat, Wyss and Duchosal[8,9]) have used a technique which they call the comparative vectorgram ("vectogramm comparatif") for the comparison of unipolar tracings. Becking, Burger and Van Milaan[1] have employed a similar technique. Neither group has exploited the method or pointed out its varied applications. This technique does not

appear to have been used by other investigators. The comparative vectorgram provides a means of continuous, instantaneous comparison of potential between two points or between two electrocardiographic leads throughout the cardiac cycle. It offers the advantage of being able to compare two wave forms of potential of the same polarity and permits immediate identification of the amplitude ratio of the two wave forms when they are truly similar.

The comparative vectorgram utilizes the principle of introducing the continuous potential differences of one lead into the X axis of the oscilloscope and the continuous potential differences of a second lead into the Y axis. If the two leads have identical wave forms of equal or opposite polarity at all times during the cardiac cycle, a straight line of 45° will be traced on the oscilloscope. As an illustration, if conventional lead I is introduced into the X axis of the oscilloscope, and is also introduced into the Y axis, a straight line inclined at 45° is formed. If the wave forms of two leads are entirely similar with a constant difference in relative amplitude, a straight line is also inscribed, but the angle of inclination will not be 45°. To illustrate, if conventional Lead I is introduced into X axis at full standard and into Y axis at half standard, a straight line is inscribed, but the angle of inclination is no longer 45°. By increasing the amplitude of one or diminishing the amplitude of the other until the amplitude of both inputs is identical, the angle of inclination can be returned to 45°.

If the two leads introduced into the X and Y axis of the oscilloscope are not similar, for example, Lead I and Lead aVf, a straight line is not inscribed and a loop is recorded. The latter, of course, is the better-known conventional vectorcardiogram which compares potential measurements from assumed perpendicular (orthogonal) leads.

This report demonstrates the use of the comparative vectorgram in evaluating three problems: 1) whether the human extremities are equipotential from their point of attachment outward; 2) whether geometric factors alone provide an adequate basis for electrically weighing or equalizing electrocardiographic leads; and 3) its use in cancellation type experiments. The first two problems illustrate the use of the comparative vectorgram in studying wave forms of the same polarity obtained from bipolar leads and the third problem illustrates the study of wave forms of opposite polarity obtained from unipolar leads.

Methods. The equipment utilized in this experiment was the same as that normally used for the recording of vectorcardiograms. A Dumont Dual-Beam Cathode Ray Oscillograph, Type 322A, was used in conjunction with Grass A.C. Preamplifiers, Model P5R. A Dumont Electronic Switch and Square Wave Generator, Type 185A, was connected to the intensity control of the oscillograph. This allowed controlled interruptions of the cathode ray beams at 400 cycles per second for timing purposes. Results were recorded with a Dumont Oscillograph Record Camera, Type 314, which allowed single frame recording of oscillograph images as well as continuous moving-film recordings.

The potentials studied in these experiments were obtained from both unipolar leads (utilizing the Wilson central terminal as a reference point) and from bipolar leads. Figure 1 shows semischematic diagrams which illustrate the manner in which these leads were devised. The potential difference (between the Wilson central terminal and a unipolar electrode, or between electrodes of a bipolar lead) which was measured by one of the leads, was used as a reference and applied to the vertical deflection plates of the oscilloscope. The electrodes of that lead remained stationary for a given group of measurements. The second lead was used as an exploring lead (or "search lead" in the terminology of Schmitt) and the potential

difference measured by it was applied to the horizontal deflection plates of the same beam. The electrodes from the latter lead were attached to various points on the torso. The comparative vectorgram was obtained by single frame pictures of this combination, the exposure time equaling the duration of one cardiac cycle. The potential difference measured by the reference or stationary lead could also be applied to the horizontal deflection plates of the second beam of the oscilloscope. This allowed simultaneous recording of the stationary and exploring lead potentials against a linear time base on a continuously-moving film strip. This latter method of recording data was utilized only in preliminary studies, since the records were felt to contain no information which was not present in the comparative vectorgram, with the exception of cardiac rate.

The electrodes used for this study were standard types used for clinical electrocardiography and vectorcardiography. It was recognized that these electrodes would produce some lack of precision, because of their relatively large size. However, this disadvantage was felt to be outweighed by the fact that the results obtained could be interpreted in the light of clinical experience and applied to clinical practices.

The subjects for this study were healthy young men with no electrocardiographic abnormalities. Subjects selected exhibited a variety of body builds and different electrical axes of the heart. All measurements were made with subjects lying in a prone or supine position, surrounded by an adequately grounded wire screen shield which diminished stray electrical interferences.

Results and Discussion. EQUIPOTENTIAL AREAS OF THE HUMAN BODY. Two assumptions have arisen in electrocardiography: that the extremities are at uniform potential, and that the potential of the extremities represents that of the point of attachment to the trunk.

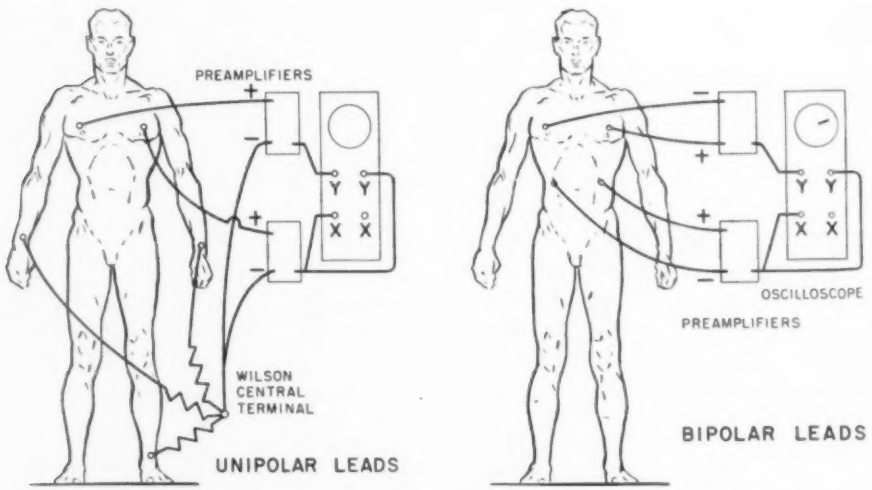

Fig. 1.—The method of derivation of the comparative vectorgram, utilizing unipolar and bipolar leads.

The assumptions arose from, and are inherent in, Einthoven's representation of the body electrically as a triangle between the shoulders and the groin.

The experiment of Wilson and Herrmann[20] is widely quoted as substantiating these assumptions. Actually those investigators attempted to show that the asymmetric location of the cardiac dipole in the thorax would not influence the direction of the deflections produced in extremity leads nor would it influence the amplitude of the deflections if the electrodes were suffi-

ciently remote. They drew a line from the fourth costal cartilage to just below Poupart's ligament on the left and divided it into four equal segments, each 5 inches in length. Then they measured the potential across each 5-inch segment individually, and showed that the amplitude progressively decreased as they moved toward the groin until there was *no* potential recorded across the most distal segment. They interpreted this to mean that the two most distal points were of the same potential. However, they seem to have made no measurements on the lower extremity, *per se*, and were not concerned with the upper extremities at all. It has also been assumed that all points below about the level of the umbilicus are essentially equipotential, but, with the exception of the experiment cited above, there appears to be no experimental basis for that assumption.

Nahum and co-workers[15] showed that, with the heart axis approaching normal, "the potential varies widely in the area of the left shoulder." With a nearly vertical heart, it is less variable. Frank[3] has also concluded that "the steep potential gradients at the left shoulder give evidence of complexity of left arm potentials as compared with other limbs." Powsner and Nahum[16] attempted to relate limb potentials with adjacent trunk potentials in the dog. They concluded that at the most proximal portion of the fore limb, the potential was intermediate in value between that of the trunk and that of the limb below the elbow where the potential was uniform. The potential below the elbow approximates the value of the potential at the junction of the middle and lower thirds of the region of attachment to the trunk. The hind limb was at an essentially uniform potential because its attachment was also at uniform potential.

The comparative vectorgram was used in this experiment to compare the wave forms of potentials recorded over the limbs and portions of the trunk. The vectorgram images remained straight lines so long as there was no detectable difference in the wave forms of the two potentials being compared. As before, the slope of the line indicated the relative amplitude of the two potentials. At 45°, their amplitudes were equal.

The technique in this experiment was to compare the customary electrocardiographic leads with experimental leads. As an example, when Lead I was the reference lead, the comparative lead might consist of a stationary right arm electrode and a left arm electrode which was progressively moved upward from the wrist to the shoulder. This permitted evaluation of the influence of changing the position of the left arm electrode by comparing the potential wave forms and amplitudes from the wrist to the shoulder.

Figure 2 illustrates the results obtained in one subject, a young male with a nearly vertical electrical axis of the heart. The shaded portion of the figure indicates the areas in which the wave form of the surface potential differs significantly from that of any of the limbs. Studies of one or more limbs in other subjects have revealed consistent results, particularly with regard to the shape of the borders. Essentially the same results have been obtained using unipolar and bipolar leads. Body build and electrical axis of the heart appeared to have little or no influence on the general configuration. The line of demarcation between the areas of similar and dissimilar wave form was rather sharply defined, with the vectorgram image rapidly opening into a wide loop when the line was crossed with the movable electrode.

Because the comparison of wave

forms of two potentials with the comparative vectorgram is more precise than the comparison of amplitude, and because minor differences were noted in the angle of inclination of the straight-line images, the actual potential *differences* over the limbs were also studied using bipolar leads. In this portion of the experiment, one electrode was fixed to the limb in the position usually used in clinical practice, while the other electrode was moved over the area previously established as having the same potential wave form. The amplitude differences obtained are indicated (in millivolts) by the lines through the unshaded portions of the figure. All measurements are with respect to the electrode at the usual clinical position on the same limb.

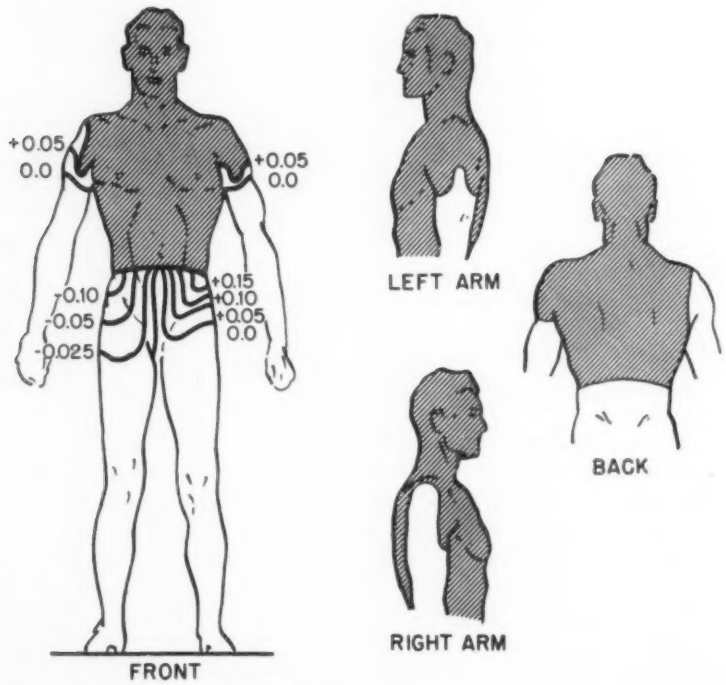

Fig. 2.—The equipotential areas of the human body. The shaded portions represent the area of the body which had a significantly different wave form from that of any extremity. In each of the unshaded areas, potential wave forms were similar. The heavy lines represent the difference in amplitude (in millivolts) of maximum potential compared to that at the usual clinical positions of electrodes (left ankle and both wrists).

GEOMETRIC LEAD LENGTH AND AMPLITUDE OF POTENTIAL. The purpose of this group of experiments was to investigate the effect of geometric lead length on the amplitude of recorded potential in a bipolar lead. It has been postulated in the past that geometric lead length on the torso surface bears a mathematical relationship to the amplitude of the potential recorded from that lead, as long as the radius distance of all electrodes remains fixed. Almost all such formulations have made a geometric assumption, that the torso is a regularly-shaped homogeneous volume conductor.

The investigations of Frank have related amplitude of recorded potentials to the length of the lead on the *image* surface[2]. He has also shown that a dipole in a homogeneous torso model (from which the image surface was constructed) creates surface potentials very similar to those of the human subject.

In order to show the application of the comparative vectorgram to this study, vertical and horizontal bipolar leads were arranged across the back of normal subjects in the positions indicated in Fig. 3. The dashed lines of the figure indicate the projections on the back of horizontal and vertical planes through the heart center. All leads were centered about these planes. In addition, these leads have the advantage of approaching very nearly true vertical and horizontal axes electrically, in terms of the image surface diagrams of Frank.

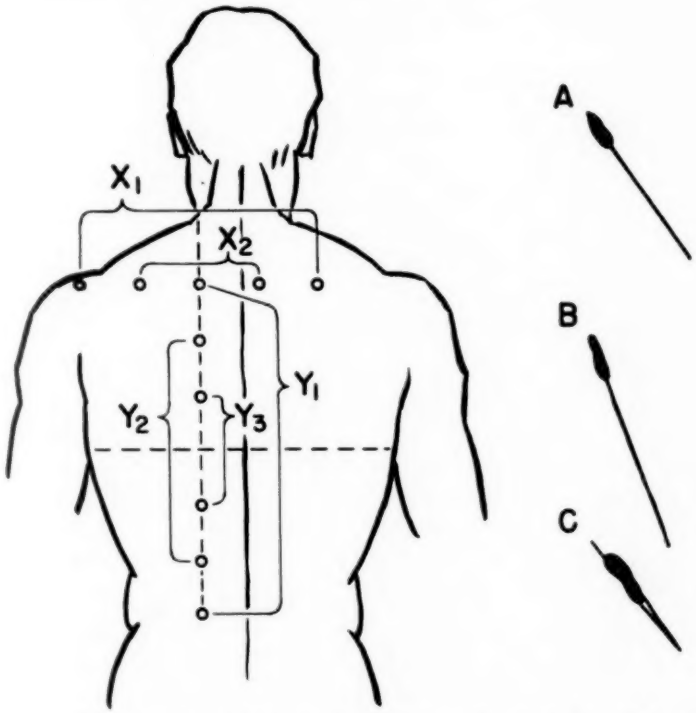

Fig. 3.—Placement of experimental bipolar leads and results obtained. Y_1 is 30 cm. long; Y_2 is 20 cm.; Y_3 is 10 cm.; X_1 is 22 cm.; and X_2 is 11 cm.

Vectorgrams *A*, *B*, and *C* are reproductions of the comparative vectorgrams obtained as follows:

Vectorgram *A*: (Y_1 on vertical axis, Y_2 on horizontal axis). Angle of inclination = 145°. Cotangent $145° = \frac{\text{horizontal}}{\text{vertical}} = 0.700$. Index of similarity = +1.000.

Vectorgram *B*: (Y_1 on vertical axis, Y_3 on horizontal axis). Angle of inclination = 161°. Cotangent 161° = 0.344. Index of similarity = +1.000.

Vectorgram *C*: (X_1 on vertical axis, X_2 on horizontal axis). Angle of inclination = 140.5°. Cotangent 140.5° = 0.824. Index of similarity = +0.955.

The comparative vectorgrams obtained by comparing these leads are shown in Figs. 3, *A*, *B*, and *C*. In Figs. 3 *A* and *B*, the wave forms are identical, and the amplitudes of the recorded potentials were closely related to the geometric lead length. The radius distance of the electrodes, it will be noted, was *not* maintained at a constant distance from the heart center, and it is perhaps fortuitous that the amplitude of potential is so closely correlated with geometric distance. Figure 3 *C* shows that the similarity of the recorded potentials across the longer and shorter horizontal leads was excellent. How-

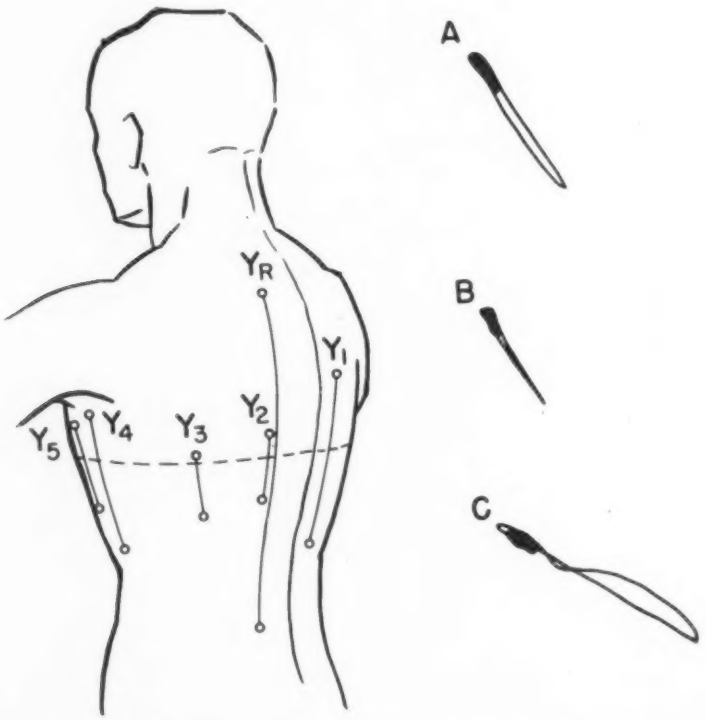

Fig. 4.—Placement of experimental bipolar leads and results obtained. The horizontal dotted line represents the level of the heart center. Leads were located about this plane as follows:

Lead Y_r (reference lead): 6″ above to 6″ below, 4 cm. left of midline.
Lead Y_1: 3″ above to 3½″ below, 22½° right of midline.
Lead Y_2: 1″ above to 2½″ below, 4 cm. left of midline.
Lead Y_3: ½″ above to 2″ below, left posterior axillary line.
Lead Y_4: 2″ above to 3½″ below, left mid-axillary line.
Lead Y_5: 1½″ above to 2″ below, left anterior axillary line.

Vectorgrams *A*, *B*, and *C* are reproductions of the comparative vectorgrams obtained as follows (with Y_r placed on the vertical axis in each):

Vectorgram *A*: (Y_1 on horizontal axis). Angle of inclination = 150°; cotangent 150° = 0.578. Y_1/Y_r (from image surface) = 0.666. Index of similarity = +0.972.

Vectorgram *B*: (Y_2 on horizontal axis). Angle of inclination = 150.5°; cotangent 150.5° = 0.566. Y_2/Y_r (from image surface) = 0.500. Index of similarity = +0.944.

Vectorgram *C*: (Y_5 on horizontal axis). Angle of inclination = 124°; cotangent 124° = 1.484. Y_5/Y_r (from image surface) = 1.000. Index of similarity = +0.988.

ever, the amplitude of the recorded potential was not as closely correlated with the geometric lead lengths.

Further investigation was done with a variety of vertical bipolar leads placed at various points around the chest. The location of these leads is shown in Fig. 4. Figures 4 *A*, *B*, and *C* show the results of several such leads compared to Y_r, a reference lead 30 cm. long, identical with lead Y_1 of Fig. 3. The location of the exploratory leads was chosen from Frank's diagram of the image surface of the homogeneous torso model, and all represent vertical electrical axes.

It will be noted that the similarity of wave forms was excellent in each case, but that the predictability of the amplitude of potential on the basis of geometric lead length is only fair and in some instances quite erroneous. This is obviously due to the fact that a fixed distance between the cardiac dipole and the center of the leads is not maintained. One lead, Y_5, just over one-fourth the length of the reference lead, records a potential whose amplitude is one and one-half times that of the reference lead.

When these lengths are considered in electrical terms, as represented on the image surface, a new relationship develops. When each of these leads is plotted on the image surface of Frank's torso model, they are all vertical leads, related in length to the reference lead (Y_r) as follows:

$Y_1 - 2/3Y_r$ $\quad$ $Y_4 - Y_r$
$Y_2 - 1/2Y_r$ $\quad$ $Y_5 - Y_r$
$Y_3 - 1/2Y_r$

Using this relationship, the predictability of recorded potential amplitude increases. The variations between results observed in our subjects and predicted from the image surface are attributed to the fact that the image surfaces of these subjects and of Frank's model do not coincide. Frank has not advanced this model's image surface as a "normal" or "standard," though several authors have used it as such. It does, however, appear to serve as a useful guide for less precise measurements. Greater precision can be obtained only by constructing image surfaces for individual subjects under study or by construction of image surfaces for large numbers of subjects in order to arrive at some estimate of relationships of image surface to physical habitus. The technique of the comparative vectorgram appears to be adaptable to such a study.

However, another interesting fact emerges from this study. Although the amplitude of the potential is not accurately predictable without the construction of an individual image surface, the shape of the potential wave form remains constant over a wide variety of lead locations. This lends further support, with limitations, to the concept that the electrical behavior of the heart closely approximates that of a dipole.

CANCELLATION EXPERIMENTS. Many of the images recorded in these experiments are elongated loops, rather than the straight lines indicative of similarity of the potential wave forms. This makes it convenient to establish a coefficient to express numerically the degree the two measured potentials depart from exact correlation. Schmitt and associates[13,18,19] have utilized a "cancellation coefficient" in order to interpret the significance of their cancellation technique. They used the following formula:

$$C = \frac{r}{Rn + S(1-n)}$$

when C is the cancellation coefficient,
r is the residual potential after best cancellation,

R is the potential at the site of the reference electrode,
S is the potential at the site of the search electrode, and
n and (1—n) are the dividing ratios of the balance potentiometer, that is, the amplification factors of the reference and search potentials, respectively.

For the sake of clarity, these abbreviations have beeen retained, instead of introducing more conventional electrical terminology. Frank[4] used a coefficient which he derived in his cancellation technique employing "balanced leads." His formula is similar in concept to that of Schmitt. Frank appeared to agree with the method which Schmitt used in calculating his coefficient, and stated that, "when the method of definition presented here is applied to Schmitt's system, assuming that the Wilson central terminal is perfect, the cancellation coefficients calculated will be slightly smaller than Schmitt's coefficients[4]."

The concept of the cancellation coefficient can readily be applied to the comparative vectorgram, and can be extended somewhat. The formulae of Schmitt and of Frank relate the residual voltage to the maximum amplitude of both the search and reference potentials. On the comparative vectorgram, "residual voltage" is represented by the maximum deviation of the oscilloscope trace from a straight line inclined at 45°. Similarly, the values of Rn and S(1—n), (that is, the product of the surface potentials and the amplification factors applied to each) are represented by the maximum vertical (Y) and horizontal (X) dimensions of the image, respectively.

Two facts become apparent: (1) The amplification factors of the two potentials need bear no relationship to one another, as they do in Schmitt's formula. For that reason, the amplification factors will be denoted "n" and "m" during further discussion. (2) In the terms of the comparative vectorgram, Schmitt's coefficient of cancellation will be smallest, indicating best cancellation, when the mean axis of the vectorgram image is inclined at a 45° angle, and thus Rn and Sm are essentially equal.

It should be noted that changes in the potentiometer setting, because of its influence on residual voltage amplification, will alter the value of the cancellation coefficients of Schmitt and Frank. This alteration is independent of that produced by electrode placement. It is felt that the influence on the coefficient of changes in the amplification factor(s) is an artificial one and that such a coefficient should ideally be influenced *only* by the location of the unipolar or bipolar leads to be compared. For this reason, Schmitt's formula has been modified to make it applicable to any vectorgram image, regardless of the angle of inclination of the image axis.

As indicated above, Rn and Sm may be considered equal when the axis of the comparative vectorgram is 45°. Also, the "residual voltage" is represented by the maximum departure (at any time during the cardiac cycle) of the vectorgram trace from a 45° axis. This departure may be measured in either the horizontal or vertical axis, since the two are equal, as indicated in Fig. 5 *A*. The effect of rotating the image axis to 45° is illustrated in Fig. 5 *B*, in which it will be noted that the departures from the 45° axis occur in both positive and negative directions, thus the "residual voltage" indicated by Schmitt's or Frank's method will become diphasic and will have reached its minimum. It is only under this condition that Schmitt's coefficient has any real meaning.

A measurement is available from the vectorgram image that cannot be otherwise obtained: the deviation of the vectorgram image from its own axis, regardless of its inclination. The importance of this is illustrated by Figs. 5 *C* and *D*. If "n" (and consequently, "Rn") is held constant, and if the position of all electrodes remains fixed, the axis of the vectorgram image can be altered by changes in "m" (and the measurement of these two values is necessary in order to obtain an index of similarity for the wave forms under examination. Note also that the value for "d" is only equal to the "residual voltage" when the image axis is 45°.

In the formula of Schmitt and of Frank, perfect cancellation is indicated by a cancellation coefficient of 0.00, although it represents perfect negative correlation between the two potentials.

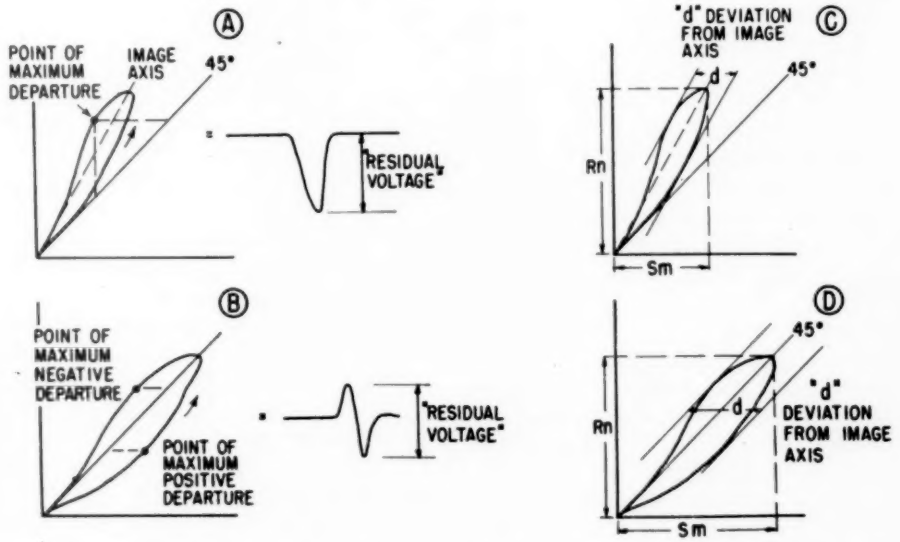

Fig. 5.—Measurement of comparative vectorgram images. (Refer to text for method of computing index of similarity.)

"Sm"). However, each change in "Sm" is reflected in a proportionate change in the horizontal deviation of the vectorgram image from its axis. Thus, the horizontal deviation, "d" and the maximum horizontal deflection of the trace, "Sm," bear a constant ratio to one another, *regardless of the angle of the axis of the vectorgram image,* and this is not influenced by amplification factors (that is, potentiometer settings). In addition, since Rn and Sm are equal at 45° the formula for "cancellation coefficient" may be rewritten as $\frac{d}{2(Sm)}$. Thus, only

On the other hand, complete lack of cancellation (that is, the residual potential equals the sum of the maximum potentials at the search and reference positions) is indicated by a cancellation coefficient of 1.00.

In this presentation, a somewhat different and perhaps more satisfying convention in terminology has been adopted. The similarity between the instantaneous wave forms of the two potentials will be denoted by an "index of similarity." Wave forms which are similar and have the same polarity will have an index of +1.00; those which

are similar but of opposite polarity will have an index of −1.00. Complete lack of similarity will be denoted by an index of similarity of 0.00.

Since the formulation for the cancellation coefficient is a measure of how dissimilar are the instantaneous wave forms, the index of similarity may be expressed as follows: $I = 1 - \frac{d}{2(Sm)}$. The index will be assigned a positive or negative value when the potentials have equal or opposite polarity, respectively.

Wave forms which are similar will be shown in the comparative vectorgram as straight lines. Wave forms which are dissimilar will be shown on the comparative vectorgram as open loops. The axis of the vectorgram image will be determined by the polarity and the relative amplitude of the two potentials. Indices of similarity which are positive (that is, where potentials have the same polarity) are shown by images that have their axes in the upper left or lower right quadrants; negative indices (that is, where potentials have opposite polarity) are shown by images that have their axes in the lower left or upper right quadrants.

Frank[4] has shown the requirements for cancellation in terms of electrical image space. It is necessary that the effective electrical axis (that is, the axis between the electrode positions on the image surface) pass through the reference point. This reference point may be established by any desired combination of two or more surface electrodes. It is well to point out, as Frank does, that the Wilson central terminal is only one possible reference point and it need bear no relationship to the center of electrical activity of the heart.

This leads to the conclusion that, in order to effect cancellation, the surface electrodes must be diametrically opposed on the image surface (though, not necessarily on the actual torso) with regard to the reference point. Surface electrodes so selected will produce a straight line image on the face of the oscilloscope, and the tangent of the angle of inclination of the straight line will be the ratio beween the lengths of the vectors joining the reference point with the electrode positions on the image surface. These factors are influenced by the resistance of the conducting tissue (and perhaps other undefined parameters) in addition to geometric distance of the leads from the center of electrical activity of the heart. This was shown by Simonson *et al.*[19], who, in making measurements of human subjects, could find no correlation when they compared ratios of amplitude of potentials recorded by unipolar leads to the ratios of the distances of the electrodes from the heart center.

Unless the axis joining the surface electrodes passes through the reference point, cancellation cannot be obtained. The index of similarity is a measure of how closely the axis joining the surface electrodes approaches the reference point. This property is not totally shared by the cancellation coefficient of Schmitt or of Frank, since the values of their coefficients is altered by changes of standardization (that is, amplification) as well as of electrode position. Thus, their coefficient locates *a point* on the axis joining the electrode positions on the image surface, and is a measure of how nearly that specific point approaches the reference point. The index of similarity formulated above, however, is concerned with the axis itself, and is a measure of how nearly *any* part of that axis approaches the reference point.

Examples of cancellations obtained

with the comparative vectorgram are shown in Fig. 6, *A* and *B*. In all cases, the potential difference recorded between the Wilson central terminal and the stationary reference electrode is shown on the vertical axis of the vectorgram. The potential difference recorded between the Wilson central terminal and the exploratory electrodes placed in the positions indicated is shown on the horizontal axis of the vectorgram. These figures illustrate how changes in position of the exploring electrode alters the shape of the vectorgram, and, consequently, alters the index of similarity of leads being compared.

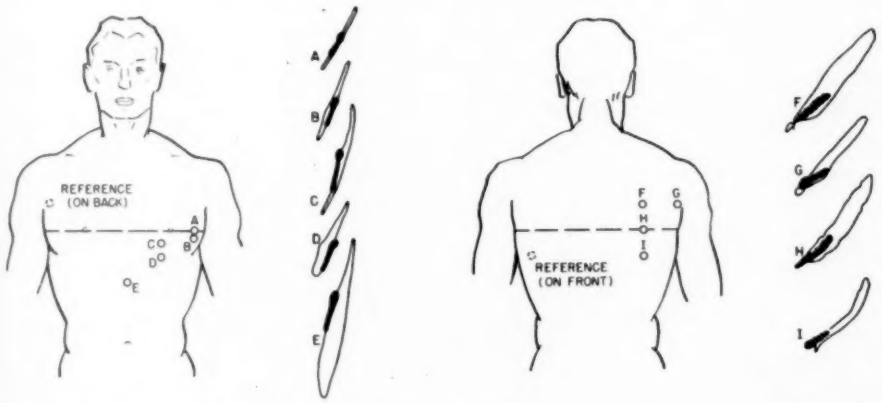

Fig. 6.—Placement of experimental unipolar leads and comparative vectorgrams obtained. Vectorgrams *F*, *G*, *H*, and *I* have been rotated to 45° by changes in amplification. See Table 1 for location of each electrode and indices of similarity.

Table 1 summarizes the location, anatomically and by Frank's coordinates, of each of the electrodes and the indices of similarity at each position of the exploratory electrode. No perfect cancellations were obtained over the precordium. However, some of the cancellations were "very good" or "excellent," as indicated by indices of similarity greater than —0.90. Electrode placement is extremely critical in the precordial area and the equipment available perhaps did not allow precise enough measurement. However, the examples here serve to illustrate the application of the method.

The results appear to coincide grossly with those of Frank[4], Schmitt *et al.*[13,18,19], and others who have found that there is a definite, but small, component in precordial potentials which cannot be cancelled at any location over the back. This is apparently due to the nearness of all or part of the myocardium to the anterior chest. Hartmann *et al.*[9] have shown that proximity potentials (that is, the portion of a potential that cannot be cancelled) may become significant (in a homogeneous volume conductor) at a distance less than twice the cardiac diameter. The problem of proximity potentials in the human body, which is a heterogeneous volume conductor with a high-resistance "shell," is in need of further study. The comparative vectorgram appears to be the superior method of investigation.

Finally, there are several findings in comparative vectorgrams which undoubtedly contain additional information concerning the behavior of the

electrical fields associated with cardiac activity. The significance of these findings, however, has not been completely elicited.

For instance, the loops which are indicative of lack of similarity of wave forms are inscribed in both clockwise and counter-clockwise directions. The directions which these loops take do not appear to be random. In Fig. 6 *A* the loop recorded at position A was clockwise, while that of position D was counter-clockwise. Moving the exploring electrode cephalad or towards the left produced less counter-clockwise or more clockwise characteristics in the loop. Movement of the exploring electrode caudad or to the right had the opposite effect. This finding was useful in locating the areas where the index of similarity was the highest. Any other significance of this finding must await more complete mapping of the human torso utilizing this technique. In addition, the index of similarity formulated in this paper, as well as the coefficients of Schmitt and of Frank, take into account only the most gross measurements of the recorded potentials, maximum amplitudes of the two potentials, the greatest disparity between the two potentials, and others. Utilizing the comparative vectorgram, it is apparent that within these limits there could be a family of curvilinear figures, infinite in number. It is not possible at the present to assess the nuances of shape and direction present in one particular curve.

It is also apparent in some of the

TABLE 1.—LOCATION OF ELECTRODE POSITIONS IN FIGURE 6A AND INDICES OF SIMILARITY

Electrode	*Anatomic Position*	*Frank's Coordinates (Approximate)*	*Index of Similarity to Potential Recorded at Reference Electrode*
Reference	2″ above heart ctr., lt. post. axill. line	5K	—
A	1½″ left of left nipple	6B	−0.907
B	½″ below "A"	½″ below 6B	−0.921
C	1″ below left nipple	½″ below 6C	−0.856
D	2″ below left nipple	7C	−0.810
E	4″ below heart ctr., anterior midline	8E	−0.704

LOCATION OF ELECTRODE POSITIONS IN FIGURE 6B AND INDICES OF SIMILARITY

Electrode	*Anatomic Position*	*Frank's Coordinates (Approximate)*	*Index of Similarity to Potential Recorded at Reference Electrode*
Reference	2″ below heart ctr., lt. ant. axill. line	7B	—
F	2″ above heart ctr., rt. midscapular line	5L	−0.773
G	2″ above heart ctr., rt. post. axill. line	5K	−0.909
H	level with heart ctr., rt. midscapular line	6L	−0.795
I	2″ below heart ctr., rt. midscapular line	7L	−0.800

images presented here that the cancellation of the depolarization (QRS) and the repolarization (T) forces are independent. This is shown in the vectorgram images by different angles of inclination of the QRS and T portions of the vectorgram. This agrees with the general findings of Schmitt[13,18,19], Langner[12], and Seiden[17]. The significance of this finding is also questionable. However, it is possible that the dipole representing repolarization forces may have a somewhat different location from that representing depolarization forces of the ventricle. Helm[10] has investigated the effect of different locations of a dipole on the shape of the electrical image surface. The relationship of the repolarization dipole, as well as the dipole of atrial excitation, to that of the depolarization forces of the ventricle is one of the problems in this field which is relatively unexplored.

Conclusions. 1. The comparative vectorgram has the unique advantage of quantitatively comparing the amplitude and polarity of one potential wave form with the amplitude and polarity of a second wave form. Commonly used methods of electrical summation reveal only differences between potential wave forms.

2. The "index of similarity" proposed in this thesis is influenced only by electrode position and not by amplification factors, an attribute not shared by other coefficients.

3. The areas below the umbilicus and distal to the middle of the upper arms in the human body may be considered equipotential in clinical practice.

4. Amplitude of potentials recorded across a bipolar lead is related to lead length in a somewhat limited sense. In the experiments reported in this paper, it was not possible to establish a firm mathematical relationship between geometric lead length and amplitude of recorded potential, because fixed distances between electrodes and heart center were not maintained.

5. No statement can be made concerning the equilibration of leads in different planes on the basis of geometric lead length alone. Image surfaces, which can be constructed by the use of the comparative vectorgram, appear to offer the only basis for such equalization.

6. The data in this thesis support the concept that the electrical behavior of the human heart approximates that of a single dipole in the thorax.

7. The comparative vectorgram substantiates the work of previous investigators who feel that there is a small but definite portion of precordial potentials which cannot be cancelled by "mirror" potentials recorded over the back. This effect is presumably due to the proximity of the myocardium to the left anterior chest wall.

8. It is not possible at present fully to interpret the "noncharacteristic" loops of the vectorgram. It is probable that more thorough analysis of these loops will reveal additional data pertaining to surface potentials and electrical fields created by the heart.

9. Much is yet to be learned about the behavior of the electrical fields created by the heart and the comparative vectorgram is an excellent tool for use in advancing this knowledge.

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SUMMARIO IN INTERLINGUA

Le Vectogramma Comparative: Un Simple Methodo Pro Le Analyse De Similaritate De Derivation

1. Le vectogramma comparative ha le unic avantage de permitter un comparation del amplitude e polaritate de un forma de unda del potential con le amplitude e polaritate de un secunde forma de unda. Le communmente usate methodos de summation electric revela solmente differentias inter formas de unda del potential.

2. Le "indice de similaritate" proponite in le presente these es influentiate solmente per le position del electrodo e non per factores de amplification. Iste attributo non es trovate in altere coefficientes.

3. Le areas infra le umbilico e distal al centro del parte superior del bracios in humanos pote esser considerate como equipotential in le practica clinic.

4. Le amplitude del potentiales registrate trans un derivation bipolar es relationate al longor del derivation in un senso plus o minus restringite. In le experimentos reportate in iste articulo, il non esseva possibile establir un firme relation mathematic inter le longor geometric del derivation e le amplitude del registrate potential, proque distantias fixe inter le electrodos e le centro del corde non esseva mantenite.

5. Il non es possibile formular conclusiones relative al equilibration de derivationes in differente planos exclusivemente super le base del longor geometric de derivationes. Superficies de imagine, construibile per medio del vectogramma comparative, pare offerer le sol base possibile pro un tal equalisation.

6. Le datos in iste these supporta le conception que le comportamento electric del corde human es un approximation del comportamento de un sol dipolo in le thorace.

(Continued on page 473)

HYPERTENSION IN ACROMEGALY

By Rudolph Balzer, M.D.*

AND

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Under appropriate experimental conditions, hypertension and hypertensive vascular disease may develop in rats given preparations of anterior pituitary containing growth hormone (Selye[7]) as well as in those given purified growth hormone (Selye[8]). Accordingly, it would be anticipated that hypertension would be a fairly common characteristic of acromegaly, a disease attributed to hypersecretion of growth hormone. From most previous reports it is not clear that such is the case. The evidence, as summarized by Raab[5], leads him to the conclusion that "reports on the blood pressure in acromegaly are rather contradictory." Thus, as reported in different series he noted: that incidences of hypertension vary from 10 to 50%; that some observers have commented on the infrequency of hypertension, describing systolic pressure levels of less than 120 mm. of Hg in about a third of the cases in two series, and that others have noted an association with hypotension together with abnormal lability of arterial pressure.

Several factors may contribute to these disparate estimates. One significant factor may be that patients with acromegaly often are first examined at a stage in the disease in which the abnormal hormonal activity has subsided but the skeletal abnormalities persist. Other important factors are lack of agreement on the levels of arterial pressure to be selected as "hypertensive," and the common concentration of interest on systolic pressure, which is more labile than diastolic pressure and which commonly is elevated in the benign "arteriosclerotic hypertension."

In view of the high incidence of cardiomegaly in acromegaly, and the possible contribution to this of diastolic hypertension, it was the purpose of our study to ascertain the range of diastolic pressure in patients with this condition and to define the presence or absence of hypertension in widely acceptable terms.

Material and Methods. Records were surveyed of 103 patients examined by one of us (E.P.McC.). The group comprised 65 women and 37 men who were diagnosed as having acromegaly, and of one boy of 11 years of age with gigantism. Ages of the adult group ranged from 19 to 68 years.

The arterial pressure selected as representative is the average of 2 or more measurements made during the period of observations. Other data noted from the charts included the presence or absence of fasting or postglucose hyperglycemia, or both, as an index of abnormal carbohydrate metabolism, and the level of serum phosphorus as an index of the activity of the disease. These data, with age and sex, are listed in Table 1.

Results. INCIDENCE OF HYPERTENSION. Of the 103 patients, in 36, diastolic pressure was 100 mm. Hg or higher

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(26 women and 10 men). The ages of these patients ranged from 33 to 62 years, averaging 48 years, as compared with an average age of 43 years in those who had diastolic pressures less than 100 mm. Hg. Reliable evidence that hypertension had preceded the onset of acromegaly was provided by one patient. The estimated duration of hypertension in the group ranged

TABLE 1.—DATA FOR 36 PATIENTS WITH ACROMEGALY AND HYPERTENSION

No.	*Sex*	*Age Years*	*Blood Pressure mm. Hg*	*Plasma Phosphorus mg./100 ml.*
1	F	54	160/100	4.9
				5.1
2	F	62	220/110	4.4
3	M	42	100/110	3.9
4	F	41	170/110	3.7
5	F	45	190/134	4.8
6	F	51	206/138	3.9
7	F	39	230/140	4.7
8	F	56	180/100	3.7
9	F	43	210/100	3.6
10	F	41	210/130	
11	F	34	184/124	2.7
				3.3
12	M	42	210/125	
13	M	46	240/155	
14	M	44	200/100	
15	F	66	160/100	3.7
				4.1
16	F	44	162/104	
17	F	68	176/108	
18	F	55	160/110	
19	F	49	190/116	3.6
				3.7
				4.8
20	M	52	180/130	3.5
21	M	45	164/100	4.7
				4.7
22	F	33	230/135	4.3
				3.7 (postop.)
23	M	60	164/114	
24	M	45	155/100	
25	M	40	160/100	3.9
26	F	28	180/110	4.9
27	F	29	180/120	
28	F	52	200/110	3.7
				4.3
29	M	55	180/110	
30	M	49	160/100	3.4
				4.3
31	F	49	200/130	4.3
				4.6
32	F	59	190/120	3.6
33	F	58	210/120	3.9
34	F	60	180/110	4.3
35	F	47	220/130	4.2
				3.3 (posttreat.)
36	F	48	212/110	4.0

from a few months to 20 years. Using the age-adjusted standards (Master, Dublin and Marks[2]), hypertension was present in 24 women and 10 men. Thus, by either criterion, the incidence of significant elevation of arterial pressure was considerably greater in these patients than in the general population.

Hypertension, when present, was more common in women (37% by Master's[3] limits) than men (26%). Of the 24 hypertensive women, 18 were in the age span of 40 to 59 years. These constituted half of the 36 women in this age range. The 27 men in this group included 9 of the 10 having hypertension. This distribution of hypertension by age and sex corresponds with previous reports (Master, Garfield and Walters[3], Ruggieri[6], and Brenning[1]); in one unselected series of patients 40 or more years of age, a diagnosis of hypertension (systolic or diastolic) was made in 60% of women and 10% of men. To examine further the possible association of hypertension in acromegaly with gonadal function, records were further scrutinized and it was found that 3 of the hypertensive women less than 40 years of age, respectively 27, 29, and 33 years old, had amenorrhea; one, aged 34 years had hot flushes and irregular menses, while one of 35 years of age described no menstrual disturbance.

ASSOCIATION WITH ABNORMAL CARBOHYDRATE AND PHOSPHORUS METABOLISM. Some disturbance of carbohydrate metabolism was found in 41 of 100 patients. Blood sugar tests were done at random times in all patients and glucose tolerance tests in some. A disturbance in carbohydrate metabolism was considered to be present in any patient in whom the blood sugar value was above 120 mg. per 100 ml., fasting or more than 3 hours after a meal or in whom any postprandial blood sugar value rose to above 170 mg. per 100 ml. Among the 41 patients with some evidence of diabetes mellitus, hypertension was present in 17 (40%), and in comparison there was hypertension in 24 of the 59 patients with normal blood sugar values (also 40%). Thus, the data do not show any association of hypertension in acromegaly with the abnormal carbohydrate metabolism common in this disease. Further, the data do not show an association of increased serum phosphorus concentration with diastolic hypertension.

COMMENT. The impression that hypertension occurs in an increased incidence in patients with acromegaly is supported by this survey, which demonstrates, by the Master limits, its presence in 34% of the patients in this series in the age range of 40 to 59 years, as compared with 10% in the working-population survey by Master, Garfield and Walters[3]. The data also confirm reports of a higher incidence of hypertension in older women than in older men and of the persistence of this distribution in acromegaly. They further suggest some association between the predisposition of acromegalic women to hypertension and failure of ovarian function, since all but one of the hypertensive acromegalic women under 40 years of age had signs of failing gonadal function.

The nature of this last association is obscure, since castrated normal women do not show an increased incidence of hypertension (Taylor, Corcoran and Page[9]), and since, also, treatment of acromegaly with estrogens (McCullagh, Beck and Schaffenburg[4]) does not influence any associated hypertension, although it may diminish serum phosphorus concentration, restore carbohydrate metabolism to normal and suppress some symptoms of the disease. However, it remains as a possibility that clinical ovarian failure may in-

crease susceptibility to any hypertensive effects of growth hormone.

Summary. A survey of levels of arterial pressure in 102 patients with acromegaly and one with gigantism demonstrated an increased incidence of arterial hypertension by the standard of average diastolic pressure of 100 mm. Hg and by the age- and sex-adjusted limits of Master, Dublin and Marks[2]. Hypertension, by the latter criterion, was present in 34% of these patients as compared with 10% in a working population. This hypertension was somewhat more common in women (37%) than men (26%); in 4 of 5 women less than 40 years of age it was associated with symptoms of gonadal failure. No association could be established between hypertension and abnormal carbohydrate metabolism or increased serum phosphorus concentration.

It is concluded that acromegaly is not characteristically associated with hypertension; it may, however, contribute to the development of hypertension in susceptible individuals.

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SUMMARIO IN INTERLINGUA

Hypertension In Acromegalia

Un studio del nivello del tension arterial in 102 patientes con acromegalia e in 1 patiente con gigantismo demonstrava un augmentate incidentia de hypertension arterial secundo le standard de un tension diastolic medie de 100 mm de Hg e secundo le limites, adjustate pro sexo e etate, de Master, Dublin, e Marks[2]. Secundo le secunde de iste criterios, hypertension esseva presente in 34% de iste patientes, in comparation con 10% constatate in un population de travaliatores. Le mentionate hypertension esseva levemente plus commun in feminas (37%) que in homines (26%). In 4 ex 5 feminas de etates de minus que 40 annos, illo esseva associate con symptomas de disfallimento gonadal. Nulle association poteva esser establite inter le hypertension e anormalitate del metabolismo de hydratos de carbon o inter le hypertension e un augmento del concentration de phosphoro in le sero.

Es concludite que acromegalia non es associate characteristicamente con hypertension. Tamen, illo pote contribuer al disveloppamento de hypertension in individuos susceptibile.

THE PERIPHERAL VASCULAR DYNAMICS OF BOWEL FUNCTION*

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Sudden death may result from the mobilization of peripheral thrombi with subsequent embolization. The incidence of fatal pulmonary embolism was found to be between 0.1 and 0.87% of surgical patients in 4 consecutive series reviewed at the Mayo Clinic (Barker, Nygaard and Priestly[1], Heard[15], Henderson[17], Wilson[29]). Ochsner[22] found that nearly 0.1% of all admissions to the New Orleans Charity Hospital from 1946 to 1950 died of pulmonary embolism. This occurrence has been reported to be even higher among medical patients than on surgical services (DeBakey[5], Ochsner[22]), particularly among those patients with congestive heart failure (Hines and Hunt[18]).

The incidence of embolism also varies considerably according to the type of surgery, disease and age of the patient. Thus, DeBakey reported[5] that the occurrence of thromboembolism was more frequent after gynecologic surgery (older women) while it was comparatively rare among obstetrical patients (younger women). Vascular thrombi and emboli are relatively frequent, and often fatal complications of myocardial infarction (Hellerstein and Martin[16], Nay and Barnes[21]). Surprisingly, thromboembolism was reported to be virtually nonexistent among paraplegics (Cook and Lyons[4]).

For pulmonary embolism to occur, there must be a detachable or freely-traveling clot originating in the right heart or venous system. Although there may be exceptions (as in cardiac septal

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defects) it has been stated (Bauer[2]) that veins of the leg and pelvis contribute 95 to 98% of such clots. Postmortem observations indicate (Hunter *et al.*[19]) that 50 to 60% of all adults carry thrombi in the plantar veins or the veins of the calf muscles. DeTakats'[6] observation that phleboliths are often seen in Roentgen-ray films of the pelvis and in veins occasionally transected during hysterectomies, points toward another possible source of such emboli.

While the exact mechanism for the mobilization of these bland thrombi is not known, it may be reasonably postulated that extreme changes in peripheral vascular caliber as well as modification of arterial and venous pressures may play a significant role in dislodging such thrombi. Gross arterial pressure variations have already been shown (Halpern, Shaftel and Selman[13]) to occur during defecation, particularly with those straining efforts initiating the Valsalva maneuver. Venous pressure and caliber changes have similarly been shown to occur during the Valsalva maneuver (Gorlin, Knowles and Storey[12], Hamilton, Woodbury and Harper[14]).

The present investigation was designed to explore the alterations of the peripheral circulation occurring in the course of bowel function and their possible influence on thrombus mobilization by studying the peripheral venous pressure, segmental and digital arterial blood flow and peripheral vascular resistance. Data were obtained from groups of normal and constipated individuals.

TABLE 1.—THE DISTRIBUTION OF VENOUS PRESSURE INCREASES OF THE ARM AND LEG DURING BOWEL FUNCTION

	Incidence of Antecubital Venous Pressure Changes						*Incidence of Saphenous Venous Pressure Changes*					
	NORMALS				*CONSTIPATED*		*NORMALS*				*CONSTIPATED*	
*Net Pressure Increase**	*Commode*		*Bedpan*		*Commode*		*Commode*		*Bedpan*		*Commode*	
mm. Hg	#	%	#	%	#	%	#	%	#	%	#	%
Above 50	—	—	—	—	—	—	2	1.6	—	—	6	5.9
41–50	—	—	4	3.3	18	19.1	5	3.9	—	—	12	11.9
31–40	2	1.8	12	9.8	14	14.9	10	7.9	4	3.4	15	14.8
21–30	6	5.5	8	6.6	7	7.4	8	6.4	13	11.0	18	17.8
16–20	17	15.5	13	10.6	11	11.7	6	4.7	4	3.4	7	6.9
11–15	11	10.0	11	9.0	18	19.2	13	10.3	7	5.9	6	5.9
6–10	16	14.5	23	18.9	14	14.9	25	19.9	28	23.7	23	22.8
1–5	58	52.7	51	41.8	12	12.8	57	45.2	62	52.6	14	13.9
Total	110	100	122	100	94	100	126	100	118	100	101	100

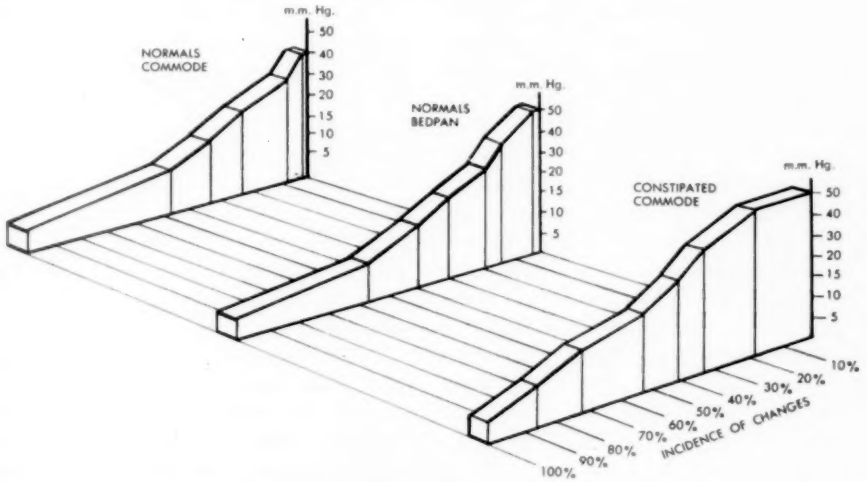
* Increased venous pressure over pre-strain level.

EXPERIMENTAL METHODS AND RESULTS.

1. *The Effect of Straining on the Peripheral Venous Pressure.* The venous pressure changes in the arm and leg were studied during 33 instances of bowel function in 16 normal individuals utilizing the commode and during 20 episodes while using the bedpan. Similar measurements were obtained from 12 constipated patients during 17 instances of defecation on the commode. Pressures were determined in both antecubital and saphenous veins.

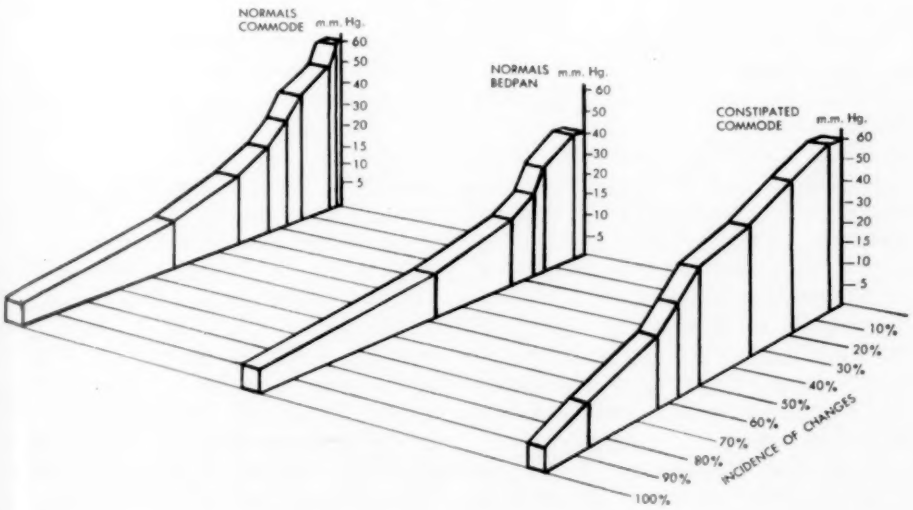
Modifications of the methods described by Moritz and Tabora[20], and

Taylor, Thomas and Schleiter[25] were used for studying the antecubital venous pressures while the technique of Pollack, Taylor, Myers and Wood[23] was adapted for measuring the saphenous vein pressure at the ankle. The venous pressures of the arm were determined with the arm extended in a plane approximately level with the right atrium. Pressures (converted to mm. Hg) were determined in each instance before defecation and used as a basis for comparison (Table 1 and Figs. 1 and 2).



THE CUMULATIVE DISTRIBUTION OF THE ANTECUBITAL VENOUS PRESSURE INCREASES DURING BOWEL FUNCTION.

Fig. 1



THE CUMULATIVE DISTRIBUTION OF THE SAPHENOUS VENOUS PRESSURE INCREASES DURING BOWEL FUNCTION.

Fig. 2

The venous pressure is approximately equal to the hydrostatic pressure exerted by a column of blood extending from the level of measurement to the third thoracic interspace at the sternum (Friedberg[9]). Postural changes, therefore, affect the venous pressure to the extent that they modify the distances between the points of determination. Thus, in the standing position, the venous pressure determined in the arm (level with the heart) will be less than that determined at the ankle. This is no longer true in the supine position, when the leg is on the same plane as the arm and the venous pressures are approximately the same for both points of determination.

The pre-strain (or resting) pressures for the entire group while sitting on the commode ranged from 4 to 11 mm. Hg (average, 8.2 mm. Hg) in the arm and from 41 to 63 mm. Hg (average, 53 mm. Hg) at the ankle. When the same subjects assumed the semi-reclining position of the bedpan, the prestrain ankle venous pressure ranged from 13 to 26 mm. Hg (average 19 mm. Hg).

Obviously the individual's posture on the commode will influence the stress on the venous system. Most individuals support the upper part of the body with the forearms resting upon the knees. The pressure of this position plus that exerted by the toilet seat, was found to impede venous return so that after 20 minutes the average resting ankle pressure rose from 53 mm. Hg to 61 mm. Hg (range, 47 to 71 mm. Hg). This may be significant to the constipated subject who generally requires extended periods of time for defecation.

There was an average of 3.3 separate elevations of venous pressure in the arm and 3.8 elevations in the leg per defecation among the normals using the commode. When the same group of normals used the bedpan, an average of 6.1 and 5.9 venous pressure elevations were determined in the arm and leg respectively. Among the group of constipated individuals the comparable average numbers of venous pressure increases were 5.5 for the arm and 5.9 for the leg (Table 1).

The greater incidence of prolonged and more intense straining episodes of the constipated group was reflected in the larger number of high venous pressure elevations when compared with the normal group at the commode (Table 1). This correlation was also apparent when the over-all venous pressure profile of the normal group using the bedpan was compared (Figs. 1 and 2) with those normals using the commode.

In the normal group at the commode, more than half of the venous pressure rises in the arm were of less than 5 mm. Hg while only 13% of the rises of the constipated group were this small. When the bedpan was used by the normal group, 42% of the increases were of this magnitude. A similar distribution was observed for the increased venous pressure in the leg.

Approximately 2% of the increased antecubital pressures of the normals at the commode and 13% of the pressure rises when using the bedpan were above 30 mm. Hg. For the constipated group, 34% of the elevated venous pressure changes of the arm were above 30 mm. Hg. In the leg, approximately 13% of the changes in venous pressure of the normal group at the commode and 33% of the increases of the constipated group were above 30 mm. Hg.

The degree of dependency of the venous system influenced the response observed. The less dependent veins of the arm exhibited smaller pressure increases than those in the leg. When the bedpan was used and with the legs in a less dependent position, 3.4% of

the rises were in this category in contrast to the 13% observed at the commode.

The duration of the individual pressure rises of the normal group was relatively short, with approximately 60% lasting less than 5 seconds (at the commode) and a similar percentage less than 7 seconds at the bedpan. The constipated subjects straining for longer periods had a greater proportion of pressure increases lasting for longer intervals. For all groups, the increased venous pressure of both the arm and the leg dropped sharply, with release of the strain, to approximately the pre-strain value within one to 4 seconds.

The changes resulting during controlled straining were studied in a group of 10 normal individuals who exerted forces varying between 20 to 60 mm. Hg by blowing against the fixed resistance of a mercury manometer. These straining efforts were maintained for periods of 25 seconds (plus or minus 3 to 5 seconds) while in a sitting position simulating defecation. The controlled strains were carried out in sequence with rest periods of at least 5 minutes between tests. The individual values were averaged (Table 2) and the mean response plotted as a function of time (Figs. 3 and 4).

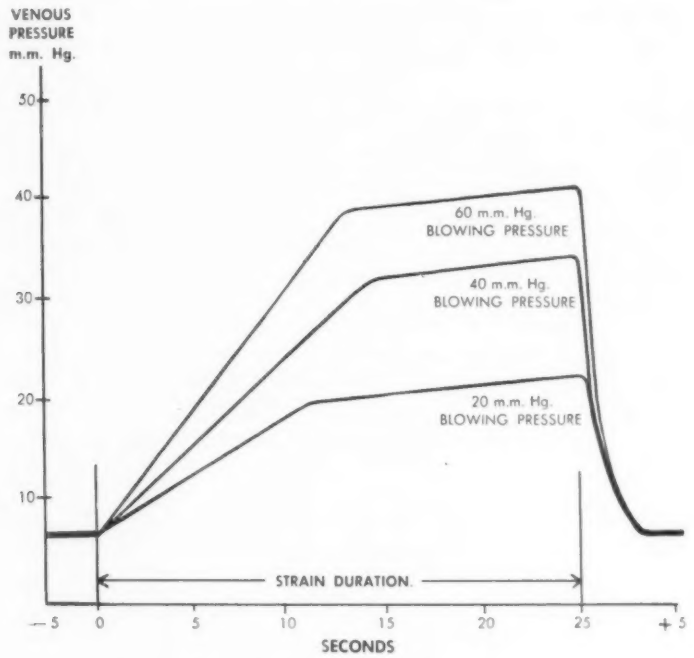
The response of the venous pressure to the controlled straining effort was observed to be more rapid in the leg than in the arm. The total net increased pressures, however, were similar for both the arm and the leg (Table 2). The greatest changes took place within the first 13 seconds in the arm and within the first 9 seconds in the leg. During any given strain, as the venous pressure increased, the unit rate of change decreased (Figs. 3 and 4). The greater straining efforts caused greater venous pressure increases; however, the net elevations were not exactly proportional to the elevated intrathoracic pressures resulting from the strains.

TABLE 2.—THE EFFECT OF CONTROLLED STRAINING ON THE PERIPHERAL VENOUS PRESSURE

Blowing Pressure mm. Hg	*Total Increase* mm. Hg*	*Venous Pressure Changes During Straining*			
		Net Change mm. Hg*	*Rate Change mm./sec.*	*Net Change* mm. Hg*	*Rate Change mm./sec.*
	ANTECUBITAL VEIN				
	25 seconds	*0–13 seconds*		*14–25 seconds*	
20	16.3	12.6	0.96	3.7	0.3
40	26.0	21.2	1.63	4.8	0.4
60	34.7	26.2	2.15	8.5	0.7
	SAPHENOUS VEIN				
	25 seconds	*0–9 seconds*		*10–25 seconds*	
20	18.2	16.0	1.7	2.2	0.14
40	31.0	25.8	2.8	5.2	0.32
60	39.0	29.4	3.3	9.6	0.60

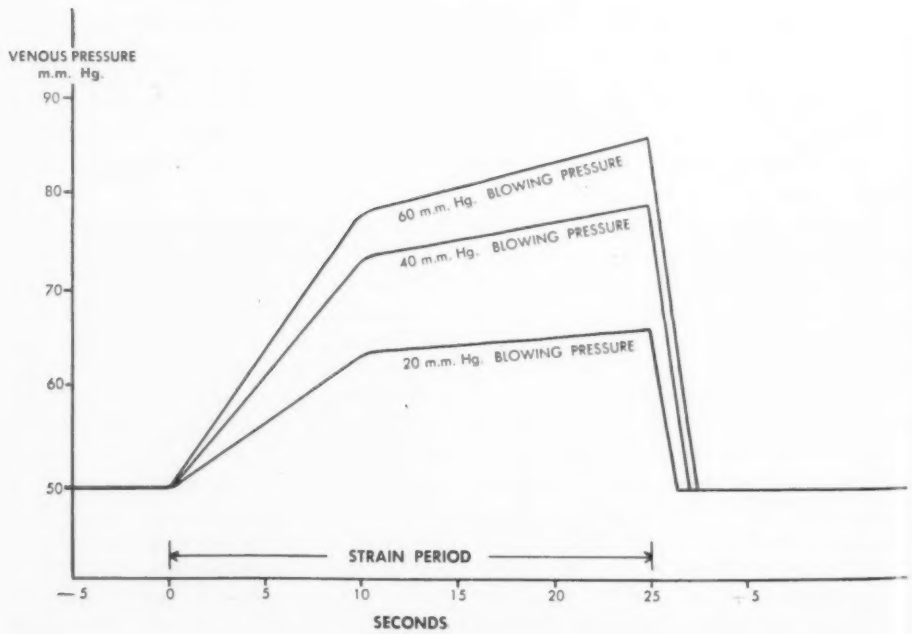
* Increase (or change) over pre-strain level.

2. *The Effects of Straining on Segmental Peripheral Blood Flow.* The blood



THE EFFECT OF CONTROLLED STRAINING ON THE ANTECUBITAL VENOUS PRESSURE.

Fig. 3



THE EFFECT OF CONTROLLED STRAINS ON THE SAPHENOUS VENOUS PRESSURE.

Fig. 4

flow through the arm and leg segments was studied in a group of 22 normal subjects during 31 instances of defecation on the commode and 28 episodes while using the bedpan. The modifying effects of the straining pattern of the constipated individual were also investigated during 23 instances of bowel function by 14 constipated subjects. The segmental blood flow data were obtained at the forearm and calf, using the Winsor Segmental Plethysmograph[30]. A paired recording (Fig. 5) of the segmental blood flow through contralateral limbs was determined for each episode of bowel function (Table 3).

It was soon apparent that motion of the limbs would produce artefacts making it impossible to interpret the data, and it therefore became necessary to stabilize and fix the position of the test limbs. A reduction in blood flow of more than 30% of the pre-strain level was considered to be a significant value. With this criterion, 19 instances of significantly reduced blood flow through both limbs were recorded for the normals at the commode and 56 decreases when the bedpan was used. The constipated series demonstrated 72 such modifications of the peripheral blood flow.

The normal group produced an average of 0.61 significant decreases in blood flow per defecation at the commode and this incidence was increased to two changes per defecation when the bedpan was used. The incidence of modification of the segmental blood flow was greatest for the constipated group, with 3.1 changes per defecation.

TABLE 3.—THE DISTRIBUTION OF THE REDUCTION IN SEGMENTAL BLOOD FLOW THROUGH THE PERIPHERAL LIMBS DURING BOWEL FUNCTION

	NORMAL				*CONSTIPATED*	
	Commode		*Bedpan*		*Commode*	
% Reduction in Minute Volume Flow	#	%	#	%	#	%
90–100	1	5.3	9	16.1	15	20.8
80–89	1	5.3	12	21.4	12	16.7
70–79	5	26.5	13	23.2	17	23.7
60–69	4	21.2	9	16.1	9	12.5
50–59	2	10.5	5	8.9	10	13.9
40–49	3	15.9	3	5.4	5	6.9
30–39	3	15.9	5	8.9	4	5.6
Total	19	100	56	100	72	100

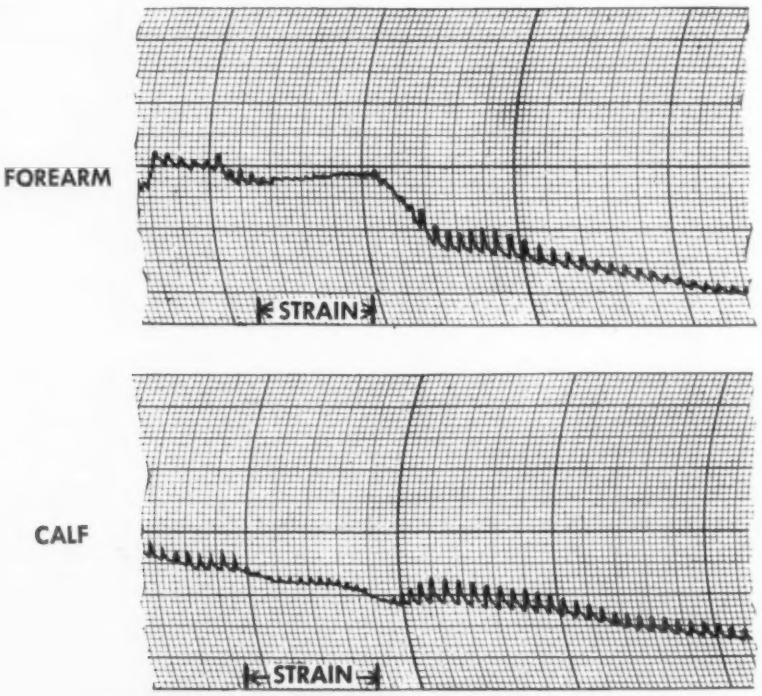
* The magnitude of the decrease in minute volume blood-flow was virtually the same for both the forearm and calf. Although the value of the calf was generally lower than that in the arm, the percentile categories included the responses of both limbs.

The average number of straining efforts per defecation was 4.2 strains at the commode and 6.3 strains with the bedpan for the normal group, and 7.8 in the constipated group. Thus, only some of the straining efforts modified the segmental blood flow, in contrast to the almost universal effect of individual strains on the venous pressure.

The resting or pre-strain blood flow through the forearm segment ranged from 2.3 ml. per 100 ml. per minute, to 6.2 ml. per 100 ml. per minute with an average of 3.7 ml. per 100 ml. per minute. For the calf segment, the pre-strain blood flow ranged from 1.8 ml. per 100 ml. per minute, to 5.8 ml. per 100 ml. per minute, with an average of

3.5 ml. per 100 ml. per minute. The peripheral blood flow dropped precipitously in both the arm and leg almost immediately with the institution of certain strains. The decrease of volume blood flow ranged from 32% to 93% of the pre-strain level in the forearm and from 34% to 96% in the calf. The magnitude of the decrease in blood flow

The magnitude of the reduction of the volume flow appeared to be related to the intensity of straining. The constipated group, which was shown (Halpern, Shaftel and Selman[13]) to have the greater incidence of higher straining efforts, had the larger incidence of episodes of diminished blood flow greater than 70% of the pre-strain



SEGMENTAL PLETHYSMOGRAPHS DURING BOWEL FUNCTION

Fig. 5.

during a single episode was approximately the same for both the forearm and calf with a range of individual differences of from 3 to 7% (average 5.3%). The calf more often had the greater decrease than the contralateral forearm. The maximal level of decreased flow was achieved within one to 4 seconds after the start of the strain and such reduction was maintained throughout the period of exertion.

level. The normal group (with less intense straining efforts) had a lesser number of such decreased blood flow episodes at the commode, but the use of the bedpan increased the frequency of reduced blood flow episodes among the normal group to approximate that of the constipated series.

A vasoconstriction was observed (Fig. 5) to follow the release of the strain, generally beginning within one

to 2 seconds and persisting for 4 to 18 seconds. The reduction of flow during this post-strain vasoconstriction, ranged from 16% to 71% of the pre-strain level for the arm and from 21% to 76% in the leg. The degree of post-strain vasoconstriction was proportional to the straining blood flow response. The greater the decrease in blood-flow during the strain period, the greater was the magnitude of the post-strain reduction in blood flow.

The duration of the post-strain vasoconstriction, however, was apparently not related to either the magnitude of this post-strain decrease of the degree of preceding reduction in flow during the strain. Thus, some episodes of post-strain vasoconstriction which caused a reduction in volume flow of approximately 65% persisted for only 3 to 5 seconds while others causing a minimal reduction of about 20 to 25%, lasted for more than 15 seconds.

The post-strain reduction in blood flow was followed by an abrupt onset of vasodilation before the pre-strain level was reestablished (Fig. 5). The magnitude of this post-strain vasodilation ranged from 110% to 205% of the pre-strain level (average 147.5%) and was evident for 3 to 14 seconds. The increased minute flow was apparently related to the intensity of the preceding vasoconstriction with the greater post-strain reductions followed by the larger increases in volume flow. There was no relationship, however, between the duration of the post-strain vasoconstriction and its succeeding vasodilation.

Since only certain of the straining efforts caused modification of the segmental blood flow, a study of the magnitude of these strains was attempted under controlled situations. The effects of controlled strains on the segmental blood flow of the forearm and calf were studied in 15 normal subjects maintaining a blowing pressure of from 10 to 60 mm. Hg against the fixed resistance of a mercury manometer while the blood flow was recorded plethysmographically. Each level of blowing pressure was maintained for a period of 20 seconds with a rest period of at least 15 minutes between successive tests. The data were recorded until the pre-strain values returned. The individual values were averaged for the group and are reported in Table 4 and Fig. 6.

TABLE 4.—THE EFFECT OF CONTROLLED STRAINING ON THE SEGMENTAL BLOOD FLOW

Blowing Pressure mm. Hg for 20 seconds	*Average Strain Response % Decrease*		*Post-Strain Vasoconstriction % Decrease*		*Post-Strain Vasodilation % Increase*	
	Forearm	*Calf*	*Forearm*	*Calf*	*Forearm*	*Calf*
10	2.2	3.1*	—	—	—	—
20	4.8	6.7*	—	—	—	—
30	45.2	51.3	30.1	34.9	113.3	121.1
40	63.1	74.2	54.1	60.2	126.1	131.2
60	88.4	92.4	63.2	74.2	140.2	168.3

* Alteration of pre-strain (or resting) average value.

It was found that those exertions capable of initiating the Valsalva maneuver were the ones principally responsible for the observed modification of segmental blood flow. The strains of lesser magnitude (10 to 20 mm. Hg) caused only minimal insignificant de-

creases in blood flow. However, with those straining efforts exceeding 30 mm. Hg, a prompt, sharp drop in volume flow was observed. The greater the straining effort, the greater was the response in diminished flow (Fig. 6). The maximal decrease was generally attained within the first 5 seconds and was maintained for the duration of the strain period.

While the magnitude of response to the straining effort was approximately the same for both upper and lower limbs, the blood flow through the calf was generally about 5 to 11% less than the forearm. The maximum reduction in minute blood flow observed during the strain period was from 45 to 88% for the arm and from 51 to 92% for the leg (Table 4).

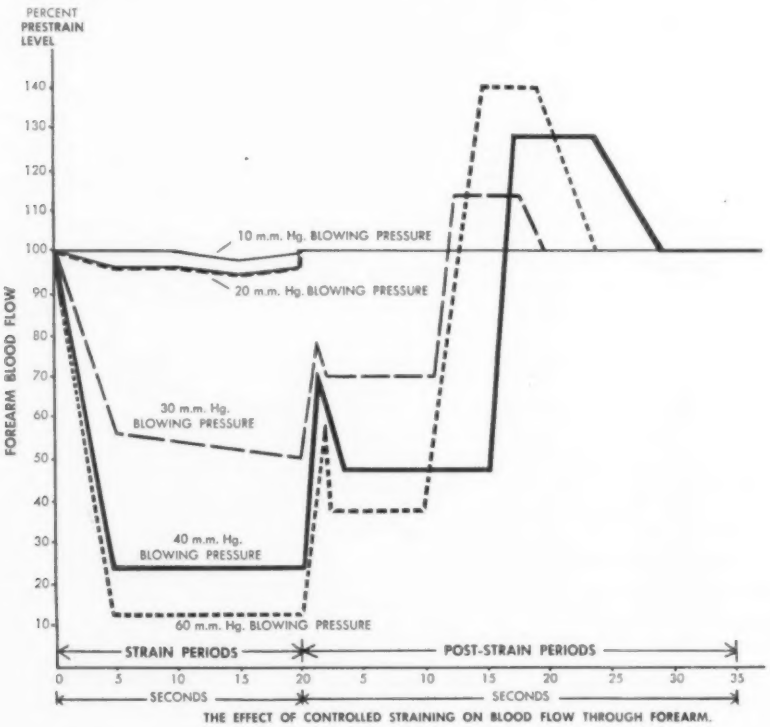


Fig. 6

With the termination of the effort, a rapid return toward the pre-strain level took place, but within one to 3 seconds a subsequent decrease in segmental flow was noted. The post-strain vasoconstriction lasted for approximately 3 to 10 seconds and was followed by a marked vasodilatation for 3 to 21 seconds, after which the blood flow finally returned to the pre-strain level.

The magnitude of the post-strain vasoconstriction was also approximately the same for both upper and lower limbs and again the greater response was observed in the legs. The diminished blood flow of the arm ranged from 30 to 63% of the pre-strain level, while for the leg, this value ranged from 35 to 74%.

Increases of from 113 to 140% of the

pre-strain blood flow were observed in the arm and from 121 to 168% increased flow observed in the leg during the post-strain vasodilatation phase. The duration of these alterations, however, were virtually the same for both the arm and the leg.

3. *The Effect of Straining on the Digital Circulation.* In order to more accurately study the effects of strains on the digital circulation, it was decided to employ controlled conditions, simulating those of actual bowel functions.

Paired digital plethysmograms were obtained from digits of contralateral limbs with the Winsor Digital Plethysmograph (Winsor, Selle and Mawardi[31]) while the subject maintained a blowing pressure of from 30 to 60 mm. Hg for a period of 20 seconds. The data, obtained from 20 individuals, were averaged to obtain a mean response for each straining level (Table 5).

The resting or pre-strain digital flow was found to range from 13.2 to 28.6 c.mm. per 4 ml. per sec. for the index finger and from 3.2 to 12.8 c.mm. per 4 ml. per sec. for the second toe. The average blood flow through the finger was 23.1 c.mm. per 4 ml. per sec. and for the toe, 9.7 c.mm. per 4 ml. per sec. The ratio of the blood flow of the toe to that of the finger was 0.42.

The volume pulsation (pulsation amplitude) for the index finger averaged 6.3 c.mm. per 4 ml. with a range of

TABLE 5.—THE EFFECT OF CONTROLLED STRAINING ON THE DIGITAL CIRCULATION

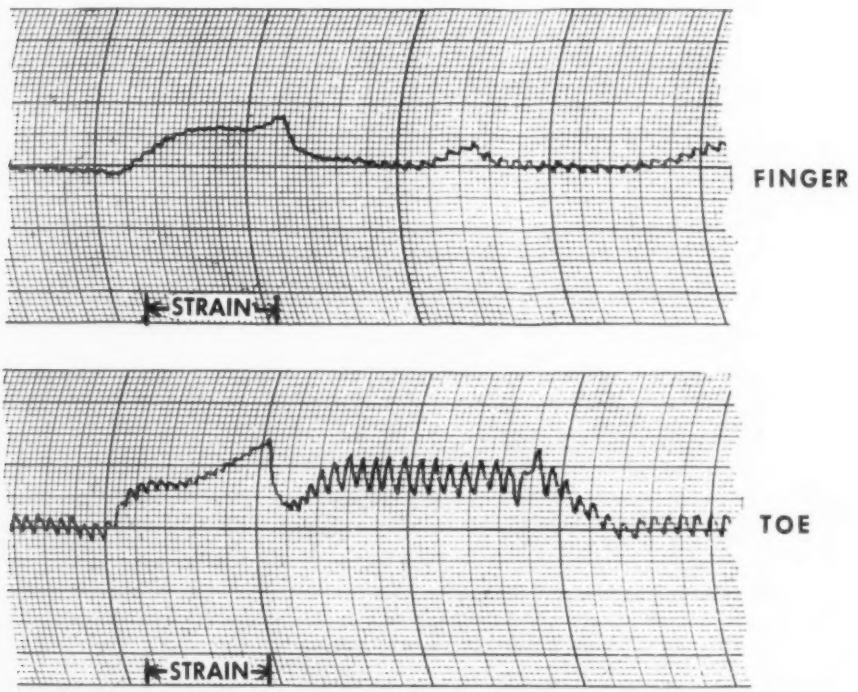
Blowing Pressure mm. Hg for 20 seconds	*Strain-Response % Decrease**		*Post-Strain Vasoconstriction % Decrease**		*Post-Strain Vasodilation % Increase**	
	Finger	*Toe*	*Finger*	*Toe*	*Finger*	*Toe*
			DIGITAL BLOOD FLOW			
30	42.3	56.9	38.4	44.1	103.2	111.4
40	79.7	88.1	56.2	61.5	115.1	123.2
60	89.2	93.2	60.9	63.1	143.9	158.1
			DIGITAL PULSATION AMPLITUDE			
30	35.5	43.3	26.1	37.1	109.1	119.2
40	72.7	82.1	50.1	58.2	124.1	135.4
60	90.1	96.4	73.2	79.4	131.2	153.2
DIGITAL BLOOD FLOW RATIO $\frac{(\text{Blood flow toe, c. mm./4 ml./sec.})}{(\text{Blood flow finger, c. mm./4 ml./sec})}$						
30	0.31		0.38		0.46	
40	0.25		0.37		0.45	
60	0.26		0.38		0.46	
PULSATION AMPLITUDE RATIO $\frac{(\text{Volume pulsation toe, c. mm./4 ml.})}{(\text{Volume pulsation finger, c. mm./4 ml.})}$						
30	0.49		0.55		0.73	
40	0.43		0.54		0.71	
60	0.24		0.53		0.75	

* Change of respective pre-strain average level. Values reported represent average for group.

from 3.8 to 9.1 c.mm. per 4 ml. and that of the toe averaged 4.1 c.mm. per 4 ml. with a range of from 2.3 to 7.6 c.mm. per 4 ml. The digital volume pulsation index (ratio of the amplitude of pulsation of the toe with that of the finger) was 0.65.

With the beginning of strain, a sharp drop in both the blood flow and pulsation volume was observed and this within the bounds of minor fluctuations, remained constant for the strain period, regardless of the duration of the exertion (Fig. 7). Lowering of digital flow was greater in the toes than in the fingers, the difference ranging from 4 to 18% with a group average of 9.2%.

The pulsation amplitude was similarly affected by the strain effort (Fig.



DIGITAL PLETHYSMOGRAPHS DURING BOWEL FUNCTION.

Fig. 7

was sustained throughout the straining period. The average decrease in the blood flow through the finger ranged from 42 to 89% of the pre-strain level and for the toe, from 57 to 93%. The greater reductions were observed after strains of higher magnitude (Table 5). The maximal drop in digital flow was achieved within one to 4 seconds and, 8 and Table 5). A decrease in pulsation volume was observed to range from 35 to 90% of the pre-strain level for the finger, and from 43 to 96% for the toe with the greater decreases occurring after the higher exertions. A large reduction in pulsation amplitude, averaging 11.3%, was observed for the toe when compared to the finger.

An abrupt rise in both digital flow and pulsation amplitude was noted immediately after the release of the strain but within one to 3 seconds this decreased with the development of a post-strain vasoconstriction. This average decrease in digital blood flow ranged between 38 and 61% for the finger and from 44 to 63% for the toe. The digital pulsation amplitude also decreased during the immediate post-straining phase. The variability of response was comparable with strains of different magnitude (Table 5). The constancy of change during the post-strain period is reflected in both the digital blood flow and digital pulsation amplitude ratios (Table 5). While there was some variability in the ratio during the strain period, there was virtually none during the post-strain period for the different levels of exertion.

Following the post strain reduction in flow, a rise in both blood flow and

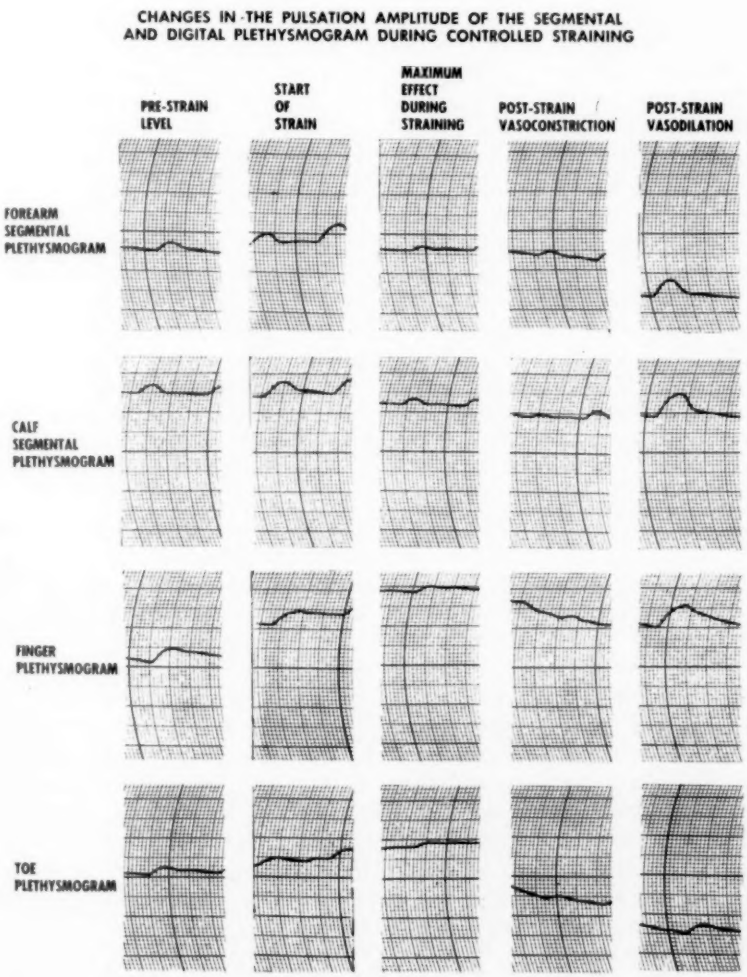


Fig. 8

pulsation amplitude occurred. Blood flow increased from 103 to 144% (of the pre-strain level) for the finger and 111 to 158% for the toe. The pulsation amplitude increased from 109 to 131% of the pre-strain level for the finger and from 119 to 153% for the toe.

A similar order of constancy was noted for the digital blood flow ratio and the digital pulsation amplitude ratio during the period of vasodilatation compared to that observed for these indices during the post-strain vasoconstriction.

4. *The Effect of Straining on the Peripheral Vascular Resistance.* The peripheral resistance, which is a function of the mean blood pressure and the segmental (or digital) blood flow, may be estimated by plethysmographic techniques. By definition (Winsor, Selle and Mawardi[31]), a unit of peripheral resistance represents the degree of resistance present when a pressure of 1 mm. Hg is exerted and the flow is 1 c.mm. per 1 ml. per sec. The *peripheral resistance unit* may be calculated with the aid of the following formula (Wiggers[26]):

$$\text{Peripheral Resistance Units} = \frac{\text{Mean Arterial Pressure, -mm. per Hg}}{\text{Digital Blood Flow, -c.mm. per 1 ml. per sec.}}$$

Since the dynamic effects of straining on the peripheral resistance are related to the progressive changes of arterial pressure and blood flow (Wiggers[26]), the effects of straining on the peripheral vascular resistance were studied in 8 subjects by simultaneous determination of the arterial blood pressure and the segmental and digital circulation during a controlled exertion (equivalent to 40 mm. Hg of intrathoracic pressure maintained for 10 seconds). The arterial blood pressure, segmental and digital blood flow were then recorded simultaneously in both the upper and lower limbs during duplicate, paired experiments. The individual values were averaged for the group and plotted against time (Fig. 9) to provide an elaboration of the effects of a standardized strain on the peripheral vascular resistance. By this procedure, a correlation between the separate phases of arterial blood pressure changes during the Valsalva maneuver and the corresponding variation in the resistance of the peripheral circulation was also obtained.

With the start of the strain (Valsalva, Phase I), an abrupt rise in blood pressure was observed and an equally sharp rise in peripheral resistance occurred as the blood flow was dramatically reduced. With the sustained reduction in volume flow, the peripheral resistance was reduced somewhat, as the pulse pressure narrowed and the arterial pressure fell. A second increase in peripheral resistance occurred during Phase II and, although the volume flow remained at virtually the same low level, the blood pressure rose as the pulse pressure continued to narrow. With the release of the strain (Phase III), both the arterial pressure and the peripheral resistance fell while the minute blood-flow increased.

The abrupt fall in blood pressure with the release of the strain, initiated a post-strain reflex vasoconstriction resulting in an increased vascular resistance which reduced the peripheral blood flow. The Phase IV, arterial blood-pressure overshoot, was soon followed by an increase in volume flow which reduced the peripheral resistance during the period of post-strain vasodilatation. The return of the blood pressure to the pre-strain level was reflected in both the peripheral resistance and volume flow which assumed their basal levels.

The dynamics of the circulations through the forearm and calf were paralleled in the finger and toe. How-

ever, while the magnitudes of the vascular changes in the arm and leg were approximately the same, they were strikingly different in the digits, with the responses in the toe being much peripheral resistance units for the toe, while that of the finger reached a peak of slightly more than 100 peripheral resistance units. The peripheral vascular resistance for both the forearm and

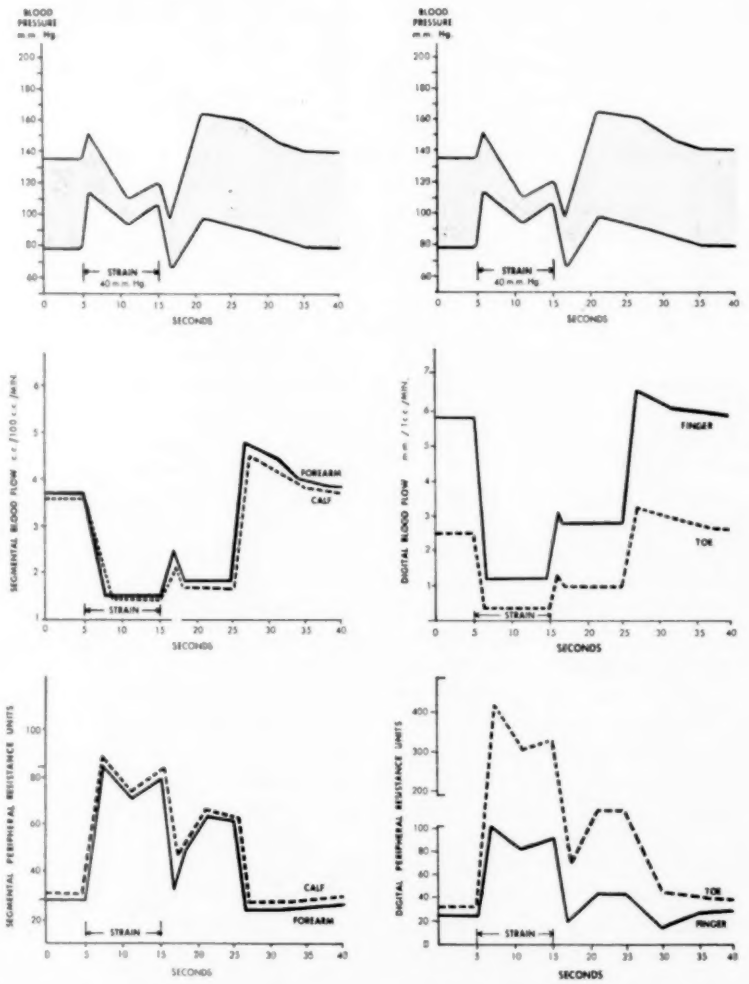


Fig. 9.—The effect of controlled straining on the peripheral vascular resistance.

more pronounced than in the finger. Thus, at peak levels, the peripheral resistance in the toe was 4 times that in the finger. The maximum resistance during straining was in excess of 400 calf was less than 100 peripheral resistance units at their peaks.

Goetz[10] postulated that blood flowed through large arteries in a pulsating manner, while that flowing through

collateral or small vessels did not exhibit this characteristic. If Goetz' theory is acceptable, a volume flow with little or no pulsation amplitude would suggest small (or collateral) vessel circulation. Thus, the ratio of the volume blood flow of the digit to the pulsation amplitude is an expression of the arterial caliber of the circulatory pathway, with an inverse ratio between this value and the relative caliber of the small conducting vessels. The normal range for this ratio, determined in the fingers and toes during a resting state by Winsor[30], was reported to fall between 1 and 5 and during vasodilatation (in normal individuals) increased only slightly to 3 to 7. In the presence of arterial disease and obstruction of the larger arteries, a high collateral circulation exists and, with secondary vasodilatation, results in ratios as high as 40 units (Winsor[30]).

The pulsation blood flow ratios determined for both the vasoconstrictive phases during and after the strain, as well as in the post-strain vasodilatation period, were all within the normal range (less than 5).This indicated a generalized reaction of the arterial pathways rather than a selective response of the larger trunk vessels.

Discussion. The peripheral circulation is subjected to a variety of stresses during normal bowel function which are exaggerated in constipated individuals. With exertions of "Valsalva magnitude," the intrathoracic pressures became elevated and impeded the venous return to the heart from the pulmonary circulation (Halpern, Shaftel and Selman[13]). This was reflected in marked, though gradual elevations, of the venous pressure.

The response of the venous pressure to straining was often slower in the upper extremities than in the lower limbs. This difference in rate of response may be attributed to the non-dependent status of the veins of the arm in contrast to those of the leg. Rushmer[24] noted similar contrasting behavior of the veins in the upper and lower limbs, during his study of the effects of modifications of the Valsalva maneuver. Our experiments, conducted with the bedpan, confirm the relationship of the dependency of the veins to the rate of venous pressure elevation during straining.

The changes in venous pressure appear to be independent of the arterial blood pressure fluctuations observed during the Valsalva maneuver (Halpern, Shaftel and Selman[13]). While the arterial blood pressure alternately rises and falls during the various phases of the Valsalva maneuver, the venous pressure maintains a continued increase throughout the entire strain period, returning to the resting state levels within seconds of termination of the strain.

This apparently uniform response of the venous circulation to sudden elevations of intrathoracic pressure becomes of special significance when both the strain and the post-strain effects on the segmental and digital blood flow are considered. Since the presence of normally functioning valves in dependent veins prevents retrograde flow of venous blood into the lower extremities, the rate of venous pressure rise depends primarily upon the rate at which blood passes through the capillaries and arteriovenous shunts. The pressure of blood in the distended veins inhibits the flow of blood from the arterial and capillary circulation and this is responsible for a lower rate of venous pressure elevation as the veins become more distended.

Another determining factor limiting the rise of venous pressure is the resistance to venous flow imposed by the elevated intrathoracic pressure. It has been noted (Hamilton, Woodbury and Harper[14]) that the increase in venous

pressure reflects the rise in intrathoracic pressure during the straining effort and rarely exceeds the pressures within the trunk. Thus, a breakthrough of the venous flow is possible when the pressure within the veins is sufficiently high. The venous "escape" would then stabilize at the pressure levels in the trunk.

The decreased segmental and digital blood flow during and immediately after the straining period as well as the post-strain vasodilatation are reflexively controlled. A reduced blood flow through the limbs and digits was observed almost immediately with the start of the strain. The response of the upper and lower limbs was qualitatively the same, although the leg and toe manifested a greater degree of response than the arm and finger. This is in contrast to the effects observed by Wilkins and Eichna[28] when, after certain sensory stimuli to the sympathetic nervous system, a different response was noted for the upper and lower limbs, even in the same individual. It would, therefore, appear that the peripheral vasoconstriction observed was the result of stimulation of pressure-sensitive nerve centers in the arterial vessels.

Thus, immediately after the first few ventricular beats exhaust the pulmonary reserve, the arterial pressure begins to fall and reflex vasoconstriction then maintains the peripheral circulation. This ultimately results in the return of arterial blood pressure (during Phase II of the Valsalva maneuver). With the subsequent profound drop in blood pressure after release of the strain (Phase III), comparable vasoreceptors respond to produce vasoconstriction. Similarly, the systolic overshoot (Phase IV), following the sudden release of the dammed up pulmonary venous blood which then returns to the left heart, is reflected in a post-strain vasodilatation. Thus, we have a vasoreflex ebb and flow in response to straining as in defecation. A similar type of response of the peripheral circulation to blood pressure variation has been observed by other investigators (Dornhorst, Howard and Leathart[8]).

The changes in segmental and digital arterial blood flow are reflections of the peripheral resistance and largely determined by vasomotor reflexes. The striking difference in the degree of peripheral resistance between the toe and finger in response to straining may offer a reasonable explanation of the greater frequency of pathologic involvement in the toe as compared with the finger.

The successive alterations of the peripheral circulatory dynamics during and after the straining accompanying bowel function, may explain the occasional dislodgement of fragmentation of a blood thrombus. Even minor changes in the velocity of the components of the flowing blood stream tend to produce disturbances (or eddies). While constriction of the vessels (Wiggers[27]) is equally capable of creating sufficient turbulence to dislodge a thrombus, the extreme fluctuation in caliber of the peripheral vessel walls during the vasoconstriction and vasodilatation phases is also capable of contributing to the freeing of loosely attached clots.

The effect of venous distention during Valsalva straining with conversion of a propagated clot into an embolus has been dramatically described by Dodd and Crockett[7]. These investigators note that "it is very easy to imagine that this sort of reflux distention and the sudden relief of distention, would produce just enough force to loosen a fragile, slightly attached, propagated clot."

The hazards arising from straining during defecation may be eliminated, to a major degree, by reducing the magnitude and duration of the straining efforts. With straining below Val-

salva requirements, noxious circulatory changes may be avoided. Such desirable reductions in the magnitude and duration of these exertions may be simply accomplished with the use of a constipation corrective (Fig. 10). After therapy with Senokot, the straining profile of a chronically constipated test group was favorably modified and,

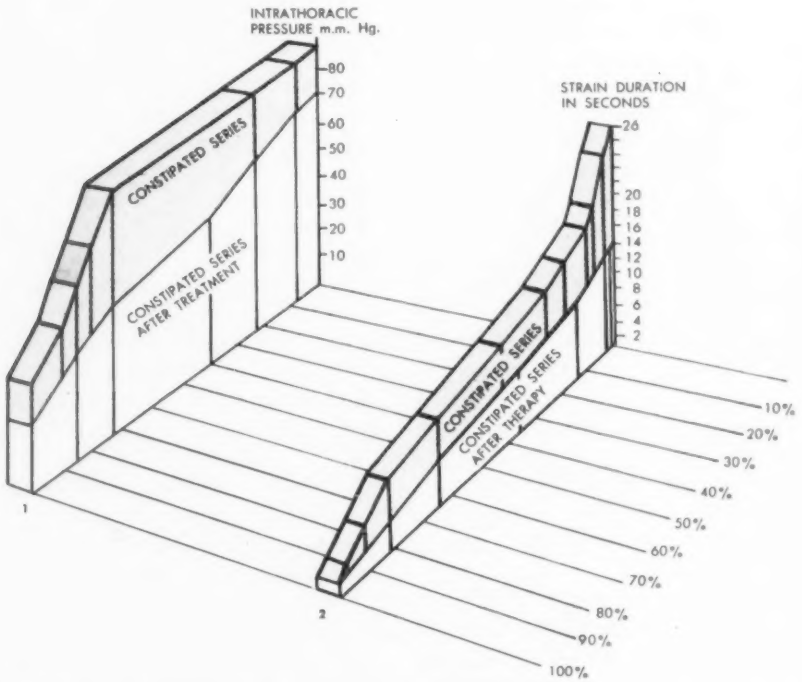


Fig. 10.—The effect of constipation correction with Senokot on the magnitude and duration of straining during defecation.

in fact, was less than that observed in the normal group. It would, therefore, appear advantageous to use a peristaltic stimulant in patients exposed to conditions leading to possible embolization.

In this connection, it is important to consider the potentially dangerous role of drug-induced constipation as a threat to the patient with cardiac or peripheral vascular disease, or both. Ganglionic blocking agents; sedatives, opiates and hypnotics (Baxter[3], Goodman and Gilman[11]), anesthetics and the manipulation of the viscera during surgery are all potent inhibitors of peristaltic activity. When the use of such drugs or surgical manipulation is necessary, the complicating side reactions should be carefully considered and steps taken to minimize their potential dangers.

The present findings emphasize the conclusion of our earlier study (Halpern, Shaftel and Selman[13]) that, if tragic cardiovascular episodes associated with defecation are to be avoided, the immediate correction of constipation is of particular importance.

Summary and Conclusions. 1. The

effect of bowel function on the peripheral circulation was studied in a group of normal and constipated subjects by observing the changes in the venous pressure and segmental blood flow. A study was also made of the effects of controlled straining on segmental blood flow, digital blood flow and peripheral vascular resistance.

2. The straining efforts associated with defecation produced an elevation of the pressure in both antecubital and saphenous veins with an abrupt return to the base value after the termination of the strain. A larger number of high venous pressure elevations were observed among the constipated group when compared with the normals. Among the normal subjects, the use of the bedpan in place of the commode, increased the incidence of higher pressure elevations in the antecubital vein, but lowered this incidence in the saphenous vein because of the lack of postural dependence of the venous system of the legs.

3. There was a sharp reduction in segmental blood flow with the onset of straining and this persisted for the period of exertion. With the release of the strain there was a transient return of blood flow toward control levels followed by a second diminution, after which a vasodilatation occurred before the return to the resting state. In response to controlled straining efforts, the venous pressure rose proportionately to the magnitude of straining.

4. During controlled exertions, the digital blood flow and pulse volume showed a pattern of change similar to that of the segmental circulation. Again, a vasoconstriction and a vasodilatation were observed following the strain period.

5. Controlled straining efforts produced a marked rise in peripheral segmental and digital vascular resistance. The response was greater in the legs and toes than in the arms and fingers. This increased resistance was terminated at the conclusion of the strain only to be followed by a sharp increase during the post-strain period.

6. Throughout the study, the fluctuations among the constipated group were of a greater magnitude and frequency than that observed among the normal subjects. This was a reflection of the greater and more profound straining efforts of the former group.

7. The implications of these findings with respect to the mobilization of peripheral thrombi and production of pulmonary embolism are discussed. The present findings emphasize the conclusion of our earlier study that, if tragic cardiovascular episodes associated with defecation are to be avoided, the immediate correction of constipation is of particular importance.

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SUMMARIO IN INTERLINGUA

Le Dynamica Periphero-Vascular Del Function Intestinal

1. Le effecto del function intestinal super le circulation peripheric esseva studiate in un gruppo de subjectos normal e constipate per observar le alterationes del tension venose e del segmental fluxo de sanguine. Esseva etiam executate un studio del effecto de controlate formas de effortio super le segmental fluxo de sanguine, le digital fluxo de sanguine, e le resistentia periphero-vascular.

2. Le effortio associate con defecation produceva un augmento del tension in le venas antecubital e in le venas saphen, sequite per un abrupte retorno al valores de base post le termination del effortio. Un plus grande numero de extreme elevationes del tension venose esseva observate in le subjectos constipate que in le subjectos normal. Inter le subjectos normal, le uso del bassino de lecto in loco del chaise perciate augmentava le incidentia del extreme elevationes de tension in le venas antecubital sed reduceva iste incidentia in le venas saphen a causa del absentia de un dependentia postural del systema venose in le gambas.

3. Il occurreva un marcate reduction in le segmental fluxo de sanguine con le initiation del effortio, e isto persisteva usque al fin del periodo del effortio. Post le relaxation del effortio, il occurreva un retorno transiente del fluxo de sanguine al nivellos de controlo. Isto esseva sequite per un secunde diminution, e postea il occurreva un vasodilatation ante le retorno al stato de reposo. In responsa a controlate grados de effortio, le tension venose montava proportionalmente con le magnitude del effortio.

4. Sub le conditiones del controlate effortio, le digital fluxo de sanguine e le volumine per pulso exhibiva un configuration de alterationes simile a illo del

circulation segmental. De novo, vasoconstriction e vasodilatation esseva observate post le periodo del effortio.

5. Grados controlate de effortio produceva un marcate elevation del resistentia vascular periphero-segmental e digital. Le responsa esseva plus intense in le gambas e digitos pedal que in le bracios e le digitos del mano. Iste augmentate resistentia esseva terminate al conclusion del effortio sed esseva sequite per un augmento acute durante le periodo post-effortial.

6. In omne partes del studio, le fluctuationes in le subjectos constipate esseva superior in magnitude e frequentia al fluctuationes observate in subjectos normal. Isto esseva un reflexion del plus intense e plus penetrante effortios del parte del constipatos.

7. Le importantia de iste constatationes es discutite con respecto al mobilisation de thrombos peripheric e al production de embolismos pulmonar. Le presente constatationes confirma e sublinea nostre previe conclusion que le desiderato de evitar tragic episodios cardiovascular in association con le effortio del defecation require le immediate correction de omne stato de constipation.

(Continued from page 448)

7. Le vectogramma comparative corrobora le conclusiones de previe investigatores qui crede que il existe un micre sed definite portion de potentiales precordial que non pote esser cancellate per potentiales "de speculo" que es registrate supra le dorso. Iste effecto es presumibilemente causate per le proximitate del myocardio al pariete thoracic sinistro-anterior.

8. Il non es possibile a iste tempore interpretar plenmente le ansas "noncharacteristic" del vectogramma. Il es probabile que un plus meticulose analyse del ansas va revelar datos additional con respecto al potentiales de superficie e al campos electric create per le corde.

9. Multo remane a apprender in le comportamento del campos electric create per le corde, e le vectogramma comparative es un excellente instrumento pro avantiar ille cognoscimentos.

A CASE REPORT OF A NEW SEROLOGICAL PATTERN IN THE RICKETTSIAL GROUP

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The rickettsial diseases of man have been classified into 4 main groups: the typhus fevers, epidemic and murine; the spotted fevers which include Rocky Mountain spotted fever, rickettsialpox, boutonneuse, African tick bite fever and several other relatively rare diseases; Q fever and finally scrub typhus. Trench fever is not definitely included in the rickettsial group.

Specific diagnosis depends upon isolation and identification of the rickettsial agent or complete studies of the host antibody response. The expected serological patterns in the rickettsial diseases with the antigens used for testing the sera from this case are outlined in Table 1.

The rickettsial disease to be reported has a serological pattern which differs from any heretofore documented, and was acquired in an area where such illnesses are unusual. The pertinent data are summarized in Table 2.

TABLE 1

RICKETTSIAL SEROLOGY								
	WEIL-FELIX ANTIGENS			COMPLEMENT-FIXATION TEST WITH RICKETTSIAL ANTIGENS				
DISEASE	OX-19	OX-2	OXK	EPIDEMIC TYPHUS SOLUBLE	EPIDEMIC TYPHUS (LEDERLE)	MURINE TYPHUS (LEDERLE)	Q	RICKETTSIALPOX SOLUBLE
TYPHUS EPIDEMIC	++++	0 or +	0	++++	0 or +	0	0	0
REGRUDESCENT (BRILL'S)	0 or ++	0	0	++++	++++	+++	0	0
MURINE	+++	0	0	+++	0 or +	+ or +++	0	0
SCRUB	0	0	++	0	0	0	0	0
ROCKY MOUNTAIN SPOTTED FEVER	+++	++	0	0	0	0	0	+++
RICKETTSIALPOX	0	0	0	0	0	0	0	++++
Q FEVER	0	0	0	0	0	0	++++	0

Case Report. A 48-year-old white housewife was admitted to the Mary Hitchcock Memorial Hospital, January 3, 1956, with a chief complaint of frontal headache of 7

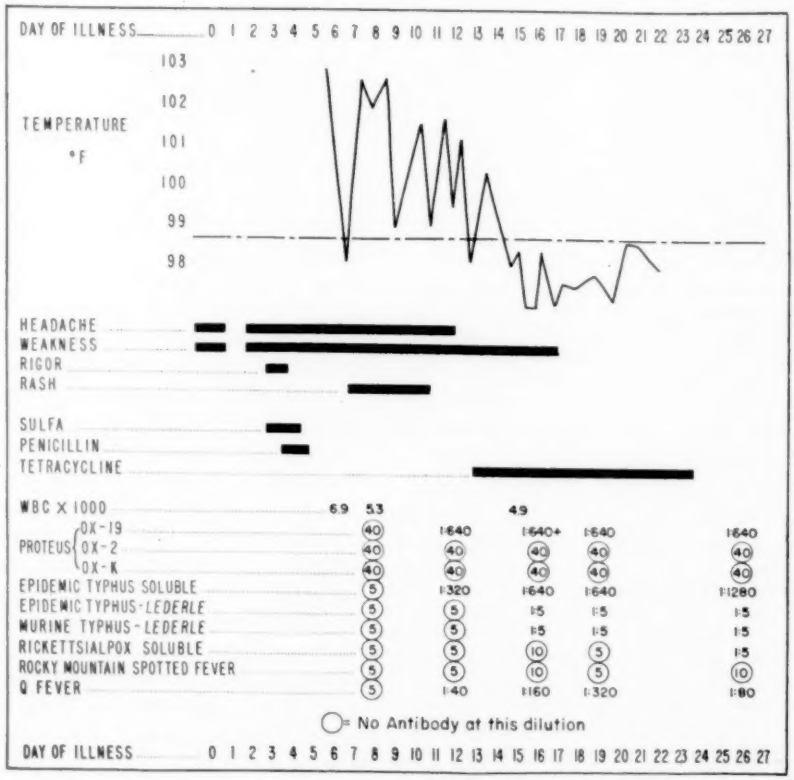
days' duration. The patient had been perfectly well until December 28, 1955, when she developed dull, persistent frontal headache while at her home in New Canaan, Connecticut. The next day she felt well enough to drive to New Hampshire, but enroute began to have stiffness of the neck, shoulders and back, malaise and a mild sore throat. On the third day anorexia, pain with eye movement, photophobia, frank chills, and a fever of 102° appeared. She was seen by a physician and given a sulfonamide preparation to take orally at 4-hour intervals. There was no response to this medication, and on the fifth day of illness she was given an intramuscular injection of penicillin, with no improvement. She was admitted to the hospital the next day, January 3, 1956. She had no specific central nervous system, genitourinary, or cardio-pulmonary symptoms. One week previous to the onset of her illness, while delousing her dogs, she was exposed to lice but saw no fleas, and was not aware of being bitten.

The patient was immunized against smallpox and typhoid fever in 1933*, prior to a trip around the world which included Mediterranean countries. She was well during this trip.

Physical examination disclosed a moderately ill patient. Her temperature was 102.6°, pulse 90, blood pressure 80/42. There was a herpes simplex lesion of the lip. She complained of soreness of the neck muscles with flexion, but there was no true rigidity. The remainder of the physical examination was normal.

Laboratory studies on the seventh day of her illness disclosed a hemoglobin of 11.4 gm., microhematocrit of 40%, white blood count, 6,950, differential count 29 stab forms,

TABLE 2


DAY OF ILLNESS 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
TEMPERATURE °F
103
102
101
100
99
98
HEADACHE
WEAKNESS
RIGOR
RASH
SULFA
PENICILLIN
TETRACYCLINE
WBC X 1000 6.9 5.3 4.9
PROTEUS OX-19 40 1:640 1:640+ 1:640 1:640
PROTEUS OX-2 40 40 40 40 40
PROTEUS OX-K 40 40 40 40 40
EPIDEMIC TYPHUS SOLUBLE 5 1:320 1:640 1:640 1:1280
EPIDEMIC TYPHUS-LEDERLE 5 5 1:5 1:5 1:5
MURINE TYPHUS-LEDERLE 5 5 1:5 1:5 1:5
RICKETTSIALPOX SOLUBLE 5 5 10 5 1:5
ROCKY MOUNTAIN SPOTTED FEVER 5 5 10 5 10
Q FEVER 5 1:40 1:160 1:320 1:80
= No Antibody at this dilution
DAY OF ILLNESS 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

*Typhus vaccine was not available until 1940.

49 polymorphonuclear neutrophils, 17 lymphocytes and 5 monocytes, platelets normal. The sedimentation rate was 77, C-reactive protein 4 mm., V.D.R.L. test nonreactive and urinalysis normal. The chest roentgenogram was normal. Agglutination tests on the eighth day of her illness for typhoid H, paratyphoid A and B, *Brucella abortus*, and *Proteus* OX19 were negative in all dilutions. Agglutination for typhoid O was positive through dilution 1:40. Total proteins 5.7 gm., albumin 3.6 gm., globulin 2.1 gm. Serum electrophoresis showed a decrease in albumin and a slight increase in the alpha-2 globulin. Thymol turbidity test was 4 units.

Tissue cultures inoculated with nasopharyngeal washings taken the eighth day of illness showed no evidence of an infectious agent. Throat cultures grew only normal organisms, and a culture of the urine grew *Escherichia coli* and *Staphylococcus albus*, coagulase negative. Stool cultures were normal. Six blood cultures were sterile and one grew *Staphylococcus albus*, coagulase negative, believed to be a contaminant.

On the seventh day of illness it was noted that the patient had about 20 discrete, pink macules without central abscesses on the arms and trunk, measuring approximately 1 cm. in diameter. These abated in 4 days and no new eruptions appeared. The patient did not improve and on the ninth day of illness a lumbar puncture was performed. The pressure, protein, cells, Kolmer and colloidal gold curve were normal or negative. Although one examiner felt the tip of the spleen at this time, there was no palpable lymphadenopathy.

On the 12th day of illness, repeat slide agglutination studies for typhoid O and H were positive 1:80; paratyphoid A, negative; paratyphoid B, positive, 1:40; Proteus OX19 was positive over 1:320. Tube dilution agglutination tests for Proteus OX19 were positive through 1:640 on the fifteenth day of illness. A diagnosis of murine typhus was made. Beginning on the thirteenth day of illness, 0.5 gm. of tetracycline was administered orally every 6 hours for 10 days. The slight improvement and temperature drop, noted the day before this medication was started, continued and the patient was discharged asymptomatic 22 days after the onset of her illness.

The serum studied by complement fixation tests in the Microbiology Department of the Harvard School of Public Health showed the following: No significant titer with epidemic typhus soluble antigen on the eighth day, a titer of 1:320 on the twelfth day, increasing to 1:1280 on the twenty-sixth day. At low dilution there was no titer with Q fever antigen on the eighth day, but by the nineteenth day a 90-fold rise was demonstrable. No significant antibody titers were obtained with rickettsialpox antigen, epidemic typhus antigen (Lederle) or murine typhus antigen (Lederle). An attempt was made to clarify the epidemiology of the illness by having blood drawn from the patient's dogs in August, 1956. A male and female dog in the family household showed a residual serologic pattern analogous to the rising titer serologic pattern of the patient. Both dogs showed no antibodies to the Rocky Mountain spotted fever group antigen. However, the female dog had a residual 1:5 antibody titer for both soluble epidemic typhus and Q fever antigen; the male dog showed a 1:20 titer to both.

Discussion. Characteristically, one might expect in classical louse-borne epidemic typhus to find elevated titers with Proteus OX19 antigen, and epidemic typhus soluble antigen, but negative results with epidemic typhus antigen (Lederle) and murine typhus antigen (Lederle) (Murray[9]). Brill-Zinsser disease is recrudescent epidemic typhus; however, the titers to Proteus OX19 are frequently absent or at a lower level than in louse-borne epidemic typhus and there is always an elevated titer with epidemic typhus antigen (Lederle) and murine typhus antigen (Lederle) (Murray[9]). Murine typhus stimulates antibodies reacting with epidemic typhus soluble antigen, murine typhus antigen (Lederle) and Proteus OX19. The antibody response to Q fever is specific for Q fever infections alone.

The clinical diagnosis made was murine typhus. However, in view of subsequent serologic data this could not be substantiated and the following possibilities were considered: (1) concomitant Q fever and epidemic typhus, (2) epidemic typhus with an anamnestic rise in Q fever antibodies, (3) Q fever with an anamnestic antibody rise to epidemic typhus, (4) recrudescent

typhus precipitated by Q fever, (5) a new rickettsial disease.

Epidemic typhus is not known to cause anamnestic rise in Q fever antibodies. Murray *et al.* found no anamnestic rise of epidemic typhus antibodies in patients suffering an attack of Q fever and having antibody evidence of previously suffering from epidemic typhus[10]. The absence of a history suggesting epidemic typhus and absence of antibodies to murine and epidemic typhus antigens (Lederle) likewise eliminates recrudescent typhus. Evidence against Q fever as the only disease is strong because antibodies reacting with Proteus OX19 and epidemic typhus antigen have been sought in Q fever but have not been found (Am. Pub. Health Assn.[1], Burnet *et al.*[2], Commission[3], Denlinger[4], Derrick[5], Geptl, Movitt and Skahen[6], Huebner, Jellison and Beck[7], Irons and Hooper[8], Robbins and Ragan[12], Spicknall *et al.*[13]). Zarafonetis has called attention to the variable antibody response in some cases of typhus fever[14]. He has noted dissociation in some cases between complement-fixing, rickettsial-agglutinating and Weil-Felix type antibodies. Two of the typhus cases studied by Zarafonetis failed to develop complement-fixing antibodies, but did produce significant rickettsial-agglutinating and Weil-Felix type antibodies. A dissociation of this sort should be considered in this case and could possibly explain the antibody pattern noted here if there were concomitant Q fever and epidemic typhus fever. This would be a rather remote possibility. The dog antibody titers suggest the possibility of a canine reservoir with dog insect vectors. This combination has not been implicated heretofore in rickettsial diseases. By process of elimination, it is surmised that this is a previously unrecognized rickettsial disease in which the causative organism shares antigens with the agents of both Q fever and typhus.

Summary. This paper reports a rickettsial disease with unusual features.

1. The disease was acquired in the Northeastern United States during the winter.

2. During the course of the disease, high complement-fixing antibody titers developed to epidemic typhus soluble antigen (1:1280) and Q fever antigen (1:320). Agglutinating antibodies to Proteus OX19 reached a high level (over 1:640). No significant complement-fixing antibody titers were obtained with rickettsialpox soluble antigen, epidemic typhus antigen (Lederle), murine typhus antigen (Lederle), or Rocky Mountain spotted fever antigen.

3. Serum specimens from 2 dogs in the family household were drawn 8 months after the illness in the patient and were found to have a low titer of complement-fixing antibodies to epidemic typhus soluble antigen and Q fever antigen.

4. This serological pattern differs from any heretofore documented. The pattern cannot be explained on the basis of any known single rickettsial disease, or even on the basis of 2 concomitant diseases unless there was failure to develop complement-fixing antibodies to some antigens.

5. It is suggested that this may be a previously unrecognized rickettsial disease in which the causative organism shares antigens with the agents of both Q fever and typhus.

ACKNOWLEDGMENT. We are indebted to Dr. Donald King for permission to report this case, and to Dr. Edward Murray and Miss Jane Driscoll, Department of Microbiology, Harvard School of Public Health, Boston, Massachusetts, for performing the complement fixation tests with rickettsial antigens.

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SUMMARIO IN INTERLINGUA

Reporto De Un Caso, Exemplificante Un Nove Patrono Serologic In Le Gruppo Rickettsial

Iste reporto concerne un caso de morbo rickettsial con characteristicas inusual.

1. Le morbo esseva acquirite al nord-est del Statos Unite durante le hiberna.

2. Durante le curso del morbo, alte titros de anticorpore a fixation de complemento se disveloppava a antigeno solubile de typhus epidemic (1:1280) e a antigeno de febre de Queensland (1:320). Le agglutinante anticorpore a Proteus OX19 attingeva un alte nivello (plus que 1:640). Nulle significative titros de anticorpore a fixation de complemento esseva obtenite per antigeno solubile de febre de Kew Garden, antigeno de typhus epidemic (Lederle), antigeno de typhus murin (Lederle), o antigeno de febre maculate del Montes Roccose.

3. Specimens de sero ab 2 canes in le menage del familia in question esseva obtenite 8 menses post le morbo del patiente. Esseva constatate que ille seros habeva un basse titro de anticorpore a fixation de complemento a antigeno solubile de typhus epidemic e a antigeno de febre de Queensland.

4. Le patrono serologic differe ab omnes previemente documentate. Illo non pote esser explicate super le base de ulle cognoscite morbo rickettsial individual o mesmo de 2 morbos concomitante, excepte si on suppone que anticorpore a fixation de complemento falleva in su formation contra le unes o le alteres del antigenos.

5. Es stipulate que isto es possibilemente un non previemente recognoscite morbo rickettsial in que le organismo causative ha antigenos in commun con le agentes tanto de febre de Queensland como etiam de typhus.

HYDROCHLOROTHIAZIDE, A NEW SALURETIC*

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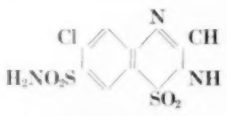
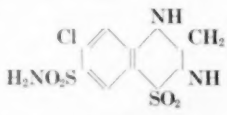
The purpose of this report is to describe experience with a new and potent saluretic compound, hydrochlorothiazide, recently synthesized by Novello and Sprague[5]. Hydrochlorothiazide is the 3,4-dihydro derivative of chlorothiazide, the 3,4-double bond in the heterocyclic ring of chlorothiazide being saturated by 2 hydrogen atoms, viz.,



Chlorothiazide
(6-chloro-7-sulfamyl, 1,2,4-benzothiadiazine-1,1-dioxide)



Hydrochlorothiazide
(6-chloro-7-sulfamyl- 3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide)

In the experimental animal, this compound produces a marked increase in excretion of sodium and chloride with relatively little increase in excretion of potassium. No significant toxicity has been found in either acute or chronic experiments in dogs.

Material and Methods. Hydrochlorothiazide was made available† in scored tablets of 50 mg. each and also in a vial containing the same amount in a lyophilized form which, when dissolved in 2 ml. of sterile water, is suitable for intravenous use.

Hydrochlorothiazide was administered orally to 15 patients listed in Table 1. All but one were males. Their ages varied from 37 to 78 years. Among these 15, there were 10 with coronary artery disease, 5 with benign essential hypertension, and one with cirrhosis and nutritional heart disease, one with phlebitis and metastatic prostatic carcinoma, one with arteriosclerosis of the aorta, and one with aortic stenosis. Cardiac enlargement of variable degree was exhibited by 11. Cardiac failure, obvious or latent, was present in 6.

Dietary sodium was limited to 200 mg. daily and a liberal fluid intake was encouraged. The dose of hydrochlorothiazide was almost always 50 mg. four times daily. In one, it was 100 mg. and in another 25 mg. four times daily. The drug was given for 2 to 24 days, for a total of 145 patient-day observations.

Fasting body weight and resting blood pressure were obtained daily. Serum sodium, potassium and chloride concentrations were determined before, after and occasionally during administration of the drug. Complete

*Supported by a grant from the Merck, Sharp and Dohme Co.

†Kindness of Dr. John R. Beem, Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania.

TABLE 1.—EFFECT OF HYDROCHLOROTHIAZIDE UPON BODY WEIGHT AND BLOOD PRESSURE

Case	*Age (Years)*	*Diagnosis*	*Cardiac Size N = Normal L = Enlarged*	*Cardiac Failure*	*Hydrochlorothiazide Dose*	*(Days)*	*Body Weight (lbs.) Before*	*After*	*Blood Pressure (mm. Hg) Before*	*After*	*Comment*
1. W.K.	47	Atherosclerosis of Aorta	N	0	50 mg. q.i.d.	9	148	149½	120/80	138/82	
2. J.F.	81	Coronary Artery Disease	L	+	50 mg. q.i.d.	8	112	103	138/82	154/70	Prompt diuresis and weight loss. No symptoms.
3. F.K.	59	Acute Myocardial Infarct.	L	0	50 mg. q.i.d.	14	157¾	147	110/78	100/80	Prompt diuresis and weight loss. No symptoms.
4. J.H.	58	Benign Hypertension (Grade 1) CVA	L	0	50 mg. q.i.d.	6	164	163	120/96	106/84	
5. J.B.	66	Coronary Artery Disease Pituitary Dwarf	L	0	50 mg. q.i.d.	8	65½	65	110/80	100/58	ECG showed increased voltage of U wave. Electrolytes normal.
6. J.W.	63	Coronary Artery Disease Benign Hypertension (Grade 1) Diabetes Mellitus.	L	0	50 mg. q.i.d.	2	191½	192	110/82	110/82	
7. G.L.	63	Coronary Artery Disease	L	0	50 mg. q.i.d.	5	158	154	188/90	140/80	
		Benign Hypertension (Grade 1)			100 mg. q.i.d.	3	156	153½	118/70	130/80	Developed hiccoughs. Serum Na fell from 137 to 125 and K from 4.8 to 3.4 mEq./L.
8. F.L.	37	Coronary Artery Disease	N								

8. F.L.	37	Coronary Artery Disease	N	0	50 mg. q.i.d.	5	150	150½	130/60	110/80	
9. J.Br.	38	Benign Hypertension (Grade 1)	N	0	50 mg. q.i.d.	8	137½	136½	148/110	134/110	
10. A.H.	77	Metastatic Prostatic Ca. Thrombophlebitis	N	0	50 mg. q.i.d.	5	111½	107	182/80	150/70	Decreased edema of legs.
11. E.R.	45	Cirrhosis. Nutritional Heart Disease	L	+	50 mg. q.i.d.	4	213	212½	140/90	150/90	
12. G.L.	58	Coronary Artery Disease	L	+	50 mg. q.i.d.	16	115	108½	115/80	110/68	Serum Na and Cl decreased from normal control to 130 and 96 mEq./L. respectively in 4 days. Drug continued without further significant change. No symptoms.
13. G.B.	63	Coronary Artery Disease Benign Hypertension (Grade 1)	L	+	50 mg. q.i.d.	15	199½	185½	260/145	150/70	
14. S.Mc	59	Coronary Artery Disease	L	+	50 mg. q.i.d.	24	170½	170	120/70	124/60	
15. S.M.	78	Coronary Artery Disease Aortic Stenosis	L	+	50 mg. b.i.d.	13	168½	163¼	210/90	170/80	

blood counts and hematocrits were also obtained frequently. Electrocardiograms were taken before and after use of the drug.

In 2 of the 15 patients, urine content of sodium, potassium and chloride was determined as a control on one day and following the oral administration of 100 mg. hydrochlorothiazide at 10 A.M. the next day. Urine samples were obtained hourly from 9 A.M. to 3 P.M. Both were on a 200 mg. sodium diet for at least one week preceding the test.

An additional 10 patients, not listed in Table 1, were given 50 to 200 mg. hydrochlorothiazide intravenously primarily to determine local effects, if any.

Results. Twelve of the 15 showed a decrease in body weight varying from one-half to 14 pounds, averaging 4.5 pounds. The remaining 3 gained weight varying from one-half to one and one-half pounds, averaging 0.8 pound. The greatest loss of weight occurred in those with edema which was either obvious or occult. Weight loss was not accompanied by any symptom other than occasional weakness. There was no instance of enervation following hydrochlorothiazide and weight loss. Rather, there was frequently a sensation of euphoria because breathing was much improved. None developed anorexia, thirst or nocturnal cramps.

Control blood pressure persistently exceeded 90 mm. Hg diastolic in 3. Of these, 2 became normotensive and one showed no change following hydrochlorothiazide therapy. The two who became normotensive lost 3 and 14 pounds of body weight and the one without change lost only one pound.

Two of the 15 developed a significant fall in the serum concentration of sodium and chloride, one with accompanying fall in serum concentration of potassium. The others showed no significant change and remained within the normal range for our laboratory.

One with a fall of serum sodium and potassium concentrations developed hiccoughs which were relieved by cessation of the drug and administration of a regular diet with prompt recovery of normal electrolyte concentrations. The other had no symptoms. In this one, the serum concentration of sodium fell to 130 mEq. per L. 4 days after onset of treatment. The drug was continued without further fall in serum concentration of sodium. There was parallel change in serum chloride concentration. Both returned to normal when the drug was stopped and regular diet given.

Electrocardiograms showed no change which could be attributed either to the drug or to its effects except possibly in one instance. This one developed more prominent U waves. However, the change in the electrocardiogram could have been due to underlying myocardial disease, for the serum concentrations of electrolytes were normal and there was no weight loss. Moreover, sequential electrocardiograms showed no significant changes when the drug was stopped.

Repeated complete blood counts and hematocrits revealed no change which could be attributed to the drug.

One patient, an 82-year-old man with pulmonary emphysema and cerebrovascular disease, not included in this series because of inability to obtain daily weight, showed a blood uric acid concentration of 8.2 mg. per 100 ml. after a total dose of 200 mg. hydrochlorothiazide with return to 5.1 mg. per 100 ml. 48 hours after cessation of the drug.

To illustrate the daily weight and blood pressure response, two cases are reported:

Case Reports. CASE 1. G.B., a 63-year-old man, complained of increasing dyspnea of several weeks' duration. Clinical and laboratory findings were consistent with hypertensive and coronary artery disease. The blood pressure was 220/110 mm. Hg and funduscopic examination revealed grade 1 changes. There was enlargement of the heart, predomi-

nantly of the left ventricle. The rate and rhythm were normal. There were no significant murmurs. The lungs were clear. There was no venous distention, hepatomegaly or edema. Electrocardiogram revealed no evidence of recent myocardial infarction. Fluorsocopy showed only enlargement of the cardiac silhouette of the left ventricular type. He was placed on a 200 mg. sodium diet and given digoxin 2.0 mg. and then 0.25 mg. once daily. Hydrochlorothiazide was given in a dose of 50 mg. q.i.d. Although he had no clinical edema, he quickly lost about 15 pounds in weight owing to diuresis and became asymptomatic. His blood pressure became normal. Serum sodium, potassium and chloride concentrations were normal before and after treatment. No symptoms occurred while on hydrochlorothiazide therapy. Figure 1 shows his daily weight and blood pressure.

COMMENT. Hydrochlorothiazide in a daily dose of 200 mg. produced a prompt diuresis with consequent disappearance of dyspnea in a 63-year-old man with hypertensive and coronary artery disease. Other than cardiac enlargement, there was no objective evidence of cardiac failure. Approximately 15 pounds of body weight could be attributed to pre-clinical edema. Following return to dry weight, no significant weight loss occurred and electrolytes remained normal despite continued administration of hydrochlorothiazide. Finally, the return of blood pressure to normal limits may have been related specifically to hydrochlorothiazide.

CASE 2. G.L., a 53-year-old Negro, was referred to Episcopal Hospital because of bilateral pleural effusion. Clinical and laboratory studies revealed findings consistent with coronary artery disease, left ventricular hypertrophy and cardiac failure. The blood pressure and fundi were normal. He was placed on a 200 mg. sodium diet and given digoxin 2.0 mg. and then 0.25 mg. once daily. Hydrochlorothiazide was given in a dose of 50 mg. q.i.d. Prompt diuresis occurred and weight decreased by approximately 10 pounds. The pleural effusion disappeared. There was no significant effect upon the blood pressure which varied within normal limits. At onset of therapy, the serum concentration of sodium was 140 mEq. per L. and

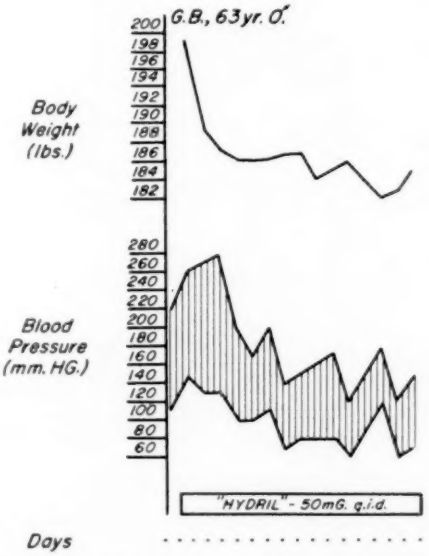


Fig. 1.—Case G.B. Daily weight and blood pressure during hydrochlorothiazide administration.

of chloride 105 mEq. per L. Four days later, these were 130 and 90 mEq. per L. respectively. The potassium concentration was normal on both occasions. Hydrochlorothiazide was continued. One week later, the serum concentration of sodium and chloride were 131 and 87 mEq. per L. respectively. Although no symptoms occurred, hydrochlorothiazide was stopped and the serum concentrations of sodium and chloride became normal. The daily weight and blood pressure are shown in Fig. 2.

COMMENT. Bilateral pleural effusion and slight cardiac enlargement were the only manifestations of cardiac failure in a 53-year-old man. Hydrochlorothiazide in a daily dose of 50 mg. q.i.d. was well tolerated and resulted in diuresis, weight loss and disappearance of pleural effusion. It did not have any hypotensive effect in the presence of a normal blood pressure. Four days following onset of hydrochlorothiazide, asymptomatic hyponatremia and hypochloremia occurred. Continued administration of hydrochlorothiazide did not result in any significant change. Following cessation of hydrochlorothiazide, the serum concentrations of sodium and of chloride became normal.

The effect in 2 patients of 100 mg. hydrochlorothiazide orally upon the urine volume and content of sodium, potassium and chloride is shown in Table 2. In the control specimens, no chloride was detected and the maximal sodium and potassium contents were 1.6 and 11.5 mEq. respectively. Following hydrochlorothiazide, the maximal contents of chloride, sodium and potassium were 29.3, 16.7 and 13.2 mEq. respectively. The average control values were: for volume, 210 ml.; for chloride, 0.0 mEq.; for sodium, 0.3 mEq.; and, for potassium, 3.1 mEq. The average values following hydrochlorothiazide were: for volume, 264 ml.; for chloride, 8.6 mEq.; for sodium, 8.0 mEq.; and, for potassium, 5.6 mEq.

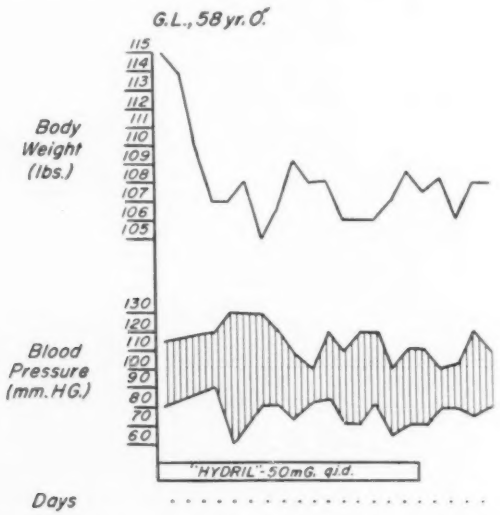


Fig. 2.—Case G.L. Daily weight and blood pressure during hydrochlorothiazide administration.

Discussion. Hydrochlorothiazide is a potent saluretic agent (Beyer[1], Mover *et al.*[4]). Following a single dose of 100 mg. orally, our studies show a marked

increase in excretion of chloride and sodium. The amount of chloride excreted exceeds that of sodium. Excretion of potassium is also increased but far less than that of sodium. Indeed, sodium is increased nearly 30-fold whereas potassium is increased less than 2-fold. The increase in urinary content of sodium, chloride and potassium following oral hydrochlorothiazide begins as early as one hour, certainly in 2 hours, and reaches a peak in 3 to 4 hours.

TABLE 2.—HOURLY URINE VOLUME AND CONTENT OF SODIUM, POTASSIUM AND CHLORIDE BEFORE AND AFTER HYDROCHLOROTHIAZIDE

Time	*Control (First Day)*				*Hydrochlorothiazide (100 mg. orally at 10 A.M.) (Next Day)*			
	Volume (ml.)	*Sodium (mEq.)*	*Potassium (mEq.)*	*Chloride (mEq.)*	*Volume (ml.)*	*Sodium (mEq.)*	*Potassium (mEq.)*	*Choridel (mEq.)*
1. Case W.U.								
9–10 A.M.	360	1.5	11.5	0.0	360	1.6	2.4	0.0
10–11 A.M.	240	1.0	3.1	0.0	120	0.6	2.1	0.0
11–12 A.M.	60	0.1	1.5	0.0	420	9.1	4.2	8.0
12–1 P.M.	60	0.1	1.5	0.0	480	16.7	13.2	29.3
1–2 P.M.	330	0.0	1.2	0.0	240	16.0	6.1	13.4
2–3 P.M.	120	0.3	4.2	0.0	270	24.7	10.8	21.3
2. Case C.G.								
9–10 A.M.	240	0.0	6.0	0.0	90	0.2	1.4	0.0
10–11 A.M.	270	0.0	1.8	0.0	120	0.1	1.2	0.0
11–12 A.M.	120	0.0	1.5	0.0	240	0.9	3.3	0.0
12–1 P.M.	240	0.0	2.3	0.0	240	2.2	6.3	3.3
1–2 P.M.	120	0.0	1.3	0.0	270	5.2	6.2	4.9
2–3 P.M.	330	0.0	3.1	0.0	240	4.9	2.1	6.0

The patients in this series were given usually 200 mg. daily in 4 divided doses. The drug was well tolerated and no symptom or sign could be attributed specifically to it in this relatively short period of observation. However, weakness occurred in one and was related to the production of hyponatremia and hypochloremia. Also, in one instance, significant hypokalemia was produced. In another, the electrocardiogram revealed a more prominent U wave than in the control but without accompanying change in serum concentration of potassium.

Although the frequency of electrolyte depletion in this series is small, its incidence is at least 10% when dietary sodium is severely limited and large doses or continued administration are prescribed. Conversely, electrolyte depletion may be avoided if dietary sodium is slightly restricted, if at all, or if small or intermittent doses are employed.

The routine use of potassium to avoid potassium depletion is usually unnecessary in the presence of an adequate dietary intake, for the amount of potassium appearing in the urine is little increased compared with the control. However, because of similarity of the drug to chlorothiazide, potassium depletion may be anticipated particularly in those with an inadequate intake, marked edema or underlying renal disease. Large doses, particularly if long continued, may also result in hypokalemia. Such dosage may be necessary

in individuals with hypertension. The development of hypokalemia under such circumstances might be a clue to an underlying aldosteroma, although we have not as yet encountered this. Finally, potassium depletion may be suspected if sequential electrocardiograms disclose increased prominence of the U wave.

The decrease in serum concentration of electrolytes, particularly potassium, may predispose the individual to the development of cardiac arrhythmias, particularly if digitalis is being used. For this reason, it is well to give minimally required rather than maximally tolerated doses of digitalis and to use a short acting preparation, like digoxin, rather than a long acting one, like digitalis or digitoxin.

Hydrochlorothiazide, like chlorothiazide (Dinon, Kim and Vander Veer[2], Oren, Rich and Belle[6]), may also produce, for unknown reason, a rise in blood uric acid. We have not as yet encountered any person who developed frank gout, although such an event has been reported following mercurial diuretics (Price[7]).

Hydrochlorothiazide, like chlorothiazide (Freis[3]), does not necessarily produce a decrease in body weight. Indeed, a decrease in weight occurs only in the presence of fluid retention which may or may not be clinically obvious. The diuresis is prompt and sustained. Although it usually exceeds that produced by mercurial diuretics, the weakness that occurs is far less and indeed may not even appear. Moreover, the person with fluid retention feels better following diuresis particularly in relief of dyspnea which occasionally is noted only in retrospect.

Hydrochlorothiazide is also an antihypertensive agent. It is not hypotensive. Blood pressure in the normal range is not lowered. Conversely, an elevated blood pressure may or may not be lowered by the drug alone. Its effect upon elevated blood pressure is unpredictable and may depend in great measure upon its saluretic effect (Freis[3]).

The drug may be given orally or intravenously. A dose of 200 mg. daily appears to be maximal, for a larger dose produces no increased diuresis. Similar observations have been reported recently by Moyer *et al.*[4]. Even 200 mg. daily is usually unnecessary and indeed may produce undesired adverse effects if long continued, particularly with restriction of sodium intake. Finally, if necessary, the drug may be given intravenously. The intravenous preparation presently available produced no local or systemic effects in a dose of 50 to 200 mg.

Conclusions. 1. Hydrochlorothiazide is a potent saluretic drug, well-tolerated orally or intravenously, producing a marked increase in excretion of sodium and chloride. The amount of chloride excreted exceeds that of sodium. Potassium excretion is relatively slightly increased. The amount of diuresis and consequent weight loss depend upon the degree of edema, which may be obvious or latent.

2. Hydrochlorothiazide, like chlorothiazide, is an antihypertensive but not a hypotensive agent.

3. Hydrochlorothiazide, like chlorothiazide, may produce hyponatremia, hypochloremia, hypokalemia, and hyperuricemia.

4. The maximal dose of hydrochlorothiazide appears to be 200 mg. daily.

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SUMMARIO IN INTERLINGUA

Hydrochlorothiazido, Un Nove Saluretico

1. Hydrochlorothiazido es un potente saluretico, ben tolerate per via oral o intravenose e producente un marcate augmento del excretion de natrium e de chloruro. Le quantitate del chloruro excernite excede illo de natrium. Le excretion de kalium es augmentate per grados relativemente leve. Le quantitate del diurese e del consequente perdita de peso depende del grado de edema, le qual pote esser obvie o etiam latente.

2. Hydrochlorothiazido, como chlorothiazido, es un antihypertensivo, sed illo non es un agente hypotensive.

3. Hydrochlorothiazido, como chlorothiazido, pote producer hyponatremia, hypochloremia, hypokalemia, e hyperuricemia.

4. Le dose maximal de hydrochlorothiazido pare esser 200 mg per die.

THE INCIDENCE OF CANCER IN CHRONIC LEUKEMIA AND IN POLYCYTHEMIA VERA

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Multiple primary malignancies have been observed and reported throughout medical literature. Warren and Gates[28] reviewed the literature prior to 1932 and found 1,259 cases of multiple malignancies reported. In a selected portion of these cases multiple primary tumors were present in 3.9% of 8,028 necropsies on cancer patients. In their own series of 1,078 necropsies on cancer cases, they found 40 cases of multiple malignancies, or an incidence of 3.7%. In a statistical analysis of the population of Massachusetts centered at the time of their study, the expected incidence of multiple cancers was 6.6 cases in males and 9.16 cases in females, while they found 15 males and 25 females with more than one primary malignancy. At the present time it is generally accepted that the incidence of primary malignancies is increased in patients with previous malignancy.

We have previously reviewed and reported on the series of patients seen at this clinic (Donner Laboratory) with chronic lymphatic leukemia[16,17], chronic myelogenous leukemia[13,17] and polycythemia vera[12,15,18]. As these series have expanded in numbers of patients and time of observation, it appeared that there were more unrelated primary malignancies associated with these conditions than could be accounted for by chance occurrence in these age groups. Therefore it was felt worthwhile to review the literature on this subject and further to analyze our own cases.

Primary malignancies in the chronic leukemias. The earliest report on the coexistence of leukemia and cancer was by Whipham[29] in 1878. In 1957 Moertel and Hagedorn[20] published an excellent and exhaustive review of the literature on the occurrence of primary malignant lesions with leukemia or lymphoma. They found a total of 194 cases which seemed to be valid examples of leukemia or lymphoma associated with another primary malignant lesion. Of these, 104 were chronic lymphatic leukemia and 17 chronic myelogenous leukemia. They added 120 cases of their own. Thirty-one of 739 chronic lymphatic leukemia patients, and 11 of 528 chronic myelogenous leukemia cases had additional malignancy. Scott[23] in 1957 reported 10 cases of malignancy with chronic lymphatic leukemia. Pisciotta and Hirschboeck[22] in 1957 reported 11 cases of primary malignancy with chronic lymphatic leukemia. In our own series, we have seen 14 primary malignancies associated with chronic lymphatic leukemia in 162 patients and 7 primary malignancies associated with chronic myelogenous leukemia in 167 patients. The location of these primary malignancies reported in

TABLE 1.—LOCATION OF PRIMARY MALIGNANCIES ASSOCIATED WITH CHRONIC LYMPHATIC LEUKEMIA AND CHRONIC MYELOGENOUS LEUKEMIA

	Chronic Lymphatic Leukemia						*Chronic Myelogenous Leukemia*			
	Moertel and Hagedorn[20] review of literature	*Moertel and Hagedorn[20] own series*	*Piciotta and Hirschbeck[22]*	*Scott[23]*	*Donner Laboratory*	*TOTAL*	*Moertel and Hagedorn[20] review of literature*	*Moertel and Hagedorn[20] own series*	*Donner Laboratory*	*TOTAL*
Skin or lips	36	8		2	7[a]	53	1	5[e]	1	7
Respiratory										
Lung or bronchus	9[b]	2	2	3	1	17	3	1		4
Larnyx	4	1	1			6				
Pleura	1					1				
Pharnyx								1		1
Gastrointestinal										
Esophagus	1	1				2				
Stomach	12	3	1		1	17	3			3
Colon or rectum	3	3	3	1	2	12	1	2[e]	1	4
Appendix	1					1				
Liver and bile ducts	1					1	1			1
Jejunum							1			1
Carcinoid	2					2				
Tongue	2			1		3				
Pancreas	3					3				
Genitourinary										
Kidney	3[b]	2	1			6	1			1
Bladder	2	2	2	1	1[a]	8		1		1
Male										
Prostate	4[c]	2	1			7		1		1
Female										
Uterine fundus		1			1	2			3	3
Uterine cervix	3				1	4	2			2
Ovary	2[d]					2	1			1
Breast—female	6	4		2	1	13	1	2		3
Melanosarcoma	4					4				
Kaposi's sarcoma	6					6	1			1
Reticulum cell sarcoma									1	1
Leiomyosarcoma	1[d]					1				
Fibrosarcoma	1[c]					1				
Bone—mandible		1				1				
Hemangio-epithelioma									1	1
Brain	1					1				
TOTAL	107	31	11	10	15	174	16	13	7	37
Number of patients	104	31	11	10	14	170	16	11	7	35

Multiple malignancies listed above:

a. Bladder and skin—1 case
b. Lung and kidney—1 case
c. Prostate and fibrosarcoma—1 case
d. Ovary and leiomyosarcoma—1 case
e. Colon or rectum and skin—2 cases

the literature and in our series is presented in Table 1. There is no indication in these reported cases that there is a predilection for any specific organ system.

Table 2 shows the incidence of primary malignancies reported in several series of chronic lymphatic leukemia and chronic myelogenous leukemia cases. The incidence in 6 chronic lymphatic leukemia series ranges from 1.2% to 18.9% with the incidence of 6.9% for the entire group of 1,281 cases. Our own series shows 8.7% incidence. In the chronic myelogenous group, the range in 4 series is 2.1% to 4.2% with the total of 2.6% incidence in 844 cases. Our series shows 4.2% incidence. In that portion of the series which have died and in which the cause of death has been determined, the incidence of associated malignancies is higher. The incidence in 259 cases of chronic lymphatic leukemia is 10.4% and in 237 cases of chronic myelogenous leukemia is 5.1%. The fairly marked difference between the 2 diseases may be explained in part by the average age at onset and the average duration of the disease. In the Donner Laboratory series reported in 1954[17], the average age at onset in chronic lymphatic leukemia was 54.5 years with an average duration of 5.4 years and a 31% seven-year survival. In chronic myelogenous leukemia, the average age at onset was 41 years with an average duration of 3.2 years and a 7-year survival rate of only 6%[13]. One would expect an increased occurrence of cancer in the older, longer lived group.

TABLE 2.—INCIDENCE OF PRIMARY MALIGNANCIES ASSOCIATED WITH CHRONIC LYMPHATIC LEUKEMIA AND CHRONIC MYELOGENOUS LEUKEMIA

	Total Series			*Deceased Only*		
	Cases of Leukemia	*Associated malignancies*		*Cases of Leukemia*	*Associated malignancies*	
Series of:		*cases*	*%*		*cases*	*%*
Chronic Lymphatic Leukemia						
Moertel and Hagedorn[20]	739	31	4.2	39	7	18.9
Pisciotta and Hirschboeck[22]	86	11	12.8	54	9	16.7
Osgood and Seaman[21]	102	12	11.8	47	2	4.3
Hoffman[11]	86	1	1.2			
Beresford[1]	106	20	18.9			
Donner Laboratory	162	14	8.7	119	9	7.6
TOTAL	1281	89	6.9	259	27	10.4
Chronic Myelogenous Leukemia						
Moertel and Hagedorn[20]	528	11	2.1	36	4	11.1
Osgood and Seaman[21]	61	2	3.3	43	2	4.7
Hoffman[11]	88	2	2.3			
Donner Laboratory	167	7	3.6	158	6	3.8
TOTAL	844	22	2.6	237	12	5.1

It is not possible to establish a "control population" to compare the incidence in these reported series with the general population. As Moertel and Hagedorn[20] point out, their series is in part selected because many of the cases were referred to the Mayo Clinic. This is even more true in our series, where all the patients have been referred with

the diagnosis of leukemia already established or strongly suspected. However, for the purpose of a rough comparison, even though it may not be statistically significant, the expected incidence of primary malignancies in a segment of the general population surviving to the same 5-year age groups as did the patients in our chronic leukemia series was estimated. Incidence figures for cancer of the skin are obviously not reflected in mortality figures, so for this comparison, skin cancers were eliminated. These calculations indicated that we might expect 2.6 deaths in a group corresponding to our chronic lymphatic leukemia patients and 0.95 deaths in a group corresponding to our chronic myelogenous leukemia patients. We had found 8 cases and 6 cases (excluding skin cancer) respectively. Even allowing for a generous "survival rate," this appeared to be a significant increase.

To obtain a more significant comparison we calculated the total patient-years of observation in our series and the occurrence of cancer cases per 1000 patient-years. The age group was determined from the average age at registration in our clinic and the average period of observation. Using the "Vital Statistics of the United States for 1949"[27] as representing the available cancer mortality figures closest to the time-center of our period of observation, we calculated the expected deaths from cancer per 1000 patient-years for the general population age group corresponding to that in our series. As Table 3 shows, the expected incidence of cancer in the chronic lymphatic leukemia age group was 3.68 cases per 1000 patient-years and in the chronic myelogenous leukemia age group was 0.95 cases per 1000 patient-years. The observed incidence of cancer with chronic lymphatic leukemia was 11.95 cases per 1000 patient-years and with chronic myelogenous leukemia was 9.68 cases per 1000 patient-years. This represents a 3-fold increase and a 10-fold increase respectively, over the predicted figures. These figures are statistically significant ($p = <0.01$) in each case.

The role of radiation exposure in the occurrence of cancer must be considered. Unfortunately, there are no large series of cases reported showing the course of untreated leukemia in relation to the development of other primary malignancy. In our series of chronic lymphatic leukemia, primary malignancy developed in 2 patients before the diagnosis of leukemia (one skin cancer and one adenocarcinoma of the pylorus) (Table 4). Twelve patients developed malignancies after diagnosis of leukemia (5 skin cancer, 6 cancers of sites other than skin, one of the skin and the bladder in the same patient). Only 2 of these patients had had no radiation therapy before the onset of the cancer (Table 5). In the chronic myelogenous series, 4 cases developed cancer before leukemia (Table 4) (one of the skin and 3 elsewhere) and 3 cases developed cancer after the leukemia and after radiation therapy, all other than skin cancer (Table 5). In the chronic lymphatic series, then, radiation could well have increased the occurrence of cancer, while in the chronic myelogenous series, more than half of the cancers occurred before any radiation therapy.

PRIMARY MALIGNANCIES IN POLYCYTHEMIA VERA. The occurrence of primary malignancies in patients with polycythemia vera has received less attention in the literature than the occurrence of additional primary malignancies in leukemia. Recently, however, one specific malignant lesion, hypernephroma, occurring with polycythemia has received more attention. One of the larger series collected from the

TABLE 3.

	Chronic Lymphatic Leukemia	*Chronic Myelogenous Leukemia*	*Polycythemia Vera*
Total patients registered	163	170	264
Total patient-years observed	586	310	1632
Age at registration—average	56.8	44.1	60.2
Years registered—average	3.6	1.8	6.1
Malignant neoplasms found—total[a]	8	6	18
Malignant neoplasms found—during registration[a]	7	3	18
Malignant neoplasms per 1000 patient-years while registered	11.95	9.68	11.03

[b]Age groups covered by average period at observation	55–59	60–64	40–44	45–49	60–64	65–69
[b]Cancer deaths in age group times 10^3	23.625	27.440	8.742	12.528	27.440	29.055
[b]Total population of age group times 10^6	7.341	6.042	9.912	9.093	6.042	4.471
[b]Cancer deaths per 1000 patient-years	3.22	4.54	.88	1.09	4.54	6.50
[b]Leukemia deaths per 1000 patient-years	.09	.13	.03	.05		
Cancer deaths less leukemia deaths per 1000 patient-years	3.13	4.41	.85	1.04		

Expected cancer deaths per 1000 patient-years—our series	3.68	.95	4.96
Approximate increase over expected cancer deaths—our series	about 3-fold	about 10-fold	about 2-fold
Probability of significance	p = < .01	p = .01	p = .001

a. excluding cancer of the skin
b. from "Vital Statistics of the United States—1949"
"cancer"-deaths from malignant neoplasms including those of the lymphatic and hematopoietic systems. leukemia-all forms of leukemia

TABLE 4.—CANCER OCCURRING PRIOR TO LEUKEMIA

	Case Number	*Sex*	*Age at Onset*		*Site of Malignancy*	
			Leukemia	*Cancer*		
Myelogenous	41–8	M	61	50	Pylorus	Died of coronary occlusion
	50–32	M	67	66	Basal cell of lip	Roentgen ray to lip prior to leukemia
	39–10	M	(1937)	(1931)	Hemangio-epithelioma	Primary in femur, metastatic to skull, Roentgen ray to local areas 6 years prior to leukemia
Lymphatic	40–19	F	71	41	Uterus	Died of coronary occlusion
	53–6	M	60	48	Recto-sigmoid	Died of leukemia and pneumonia
	57–65	F	56	49	Basal cell, nose	Local Roentgen ray to nose prior to leukemia

TABLE 5.—CANCER OCCURRING AFTER ONSET OF LEUKEMIA

	Case Number	Sex	Age at Onset: Leukemia	Age at Onset: Cancer	Site of Malignancy	Radiation Therapy Prior to Cancer: P-32: Amount	P-32: Time started prior to cancer	Roentgen-ray or Other: Site and kind	Roentgen-ray or Other: Time prior to cancer	
Chronic Lymphatic Leukemia	40–1	M	49	74	Rectum	23.5 mc.	12 yrs.	—	—	
	41–3	F	59	67	Breast	26.6 mc.	8 yrs.	—	—	
	45–2	M	71	75	Basal cell, face	15.4 mc.	4 yrs.	—	—	
				76	Bladder	17.4 mc.	5 yrs.	—	—	
	46–22	M	59	63	Basal cell, face	5.5 mc.	4 yrs.	Roentgen-ray to spleen	4 yrs.	
	48–30	M	69	72	Squamous cell, face	4.0 mc.	1 mo.	Y^{90} 4 mc., i.v.	1 yr.	
	49–1	F	67	70	Cervix uteri	4.0 mc.	10 mos.	—	—	
	49–7	M	59	65	Basal cell, back	4.0 mc.	5 mos.	Radium to naso-pharynx	3 yrs.	
	49–9	F	58	68	Endometrium	4.0 mc.	10 yrs.	Radium to uterus	12 yrs.	
	46–20	M	57	58	Cecum	—	—	Total body Roentgen-ray	1 yr.	No P-32
	56–12	M	70	72	Lung	—	—	Roentgen-ray to abdomen	1 yr.	
	42–54	M	49	52	Basal cell, face	—	—	—	—	No Radiation
	49–2	M	71	71	Basal cell, face	—	—	—	—	
Chronic Myelogenous Leukemia	46–42	F	57	61	Uterus (fundus)	15.0 mc.	14 mos.	—	—	
	48–5	F	35	43	Uterus (fundus)	3.0 mc.	6 yrs.	—	—	
	51–62	F	59	60	Reticulum cell sarcoma	27.0 mc.	10 mos.	—	—	

literature and from his experience is that of Forssell[6,7]. Damon and others[4] in 1958 reviewed the reports of Forssell and added several cases of their own. We have also reviewed the literature and reported on this subject[14] as have others (Conley, Kowal and D'Antonio[2], Frey[8]).

Videbaek[26] in 1950 reported on a series of 35 necropsies in 125 patients with polycythemia vera who had not received radioactive phosphorus therapy. He found 8 primary malignancies in these 35 necropsies and an additional patient still living with hypernephroma. He calculated that the expected deaths from cancer for this time and age group should have been 3 cases. Stroebel, Hall and Pease[24] in 1951 reported a series of 32 patients who did not receive radiophosphorus and in which the cause of death was known. There were 4 deaths from malignancy in this group in patients who had received no radiation of any kind. Stroebel and Law[25] in 1956 from the same clinic reported 241 patients treated with P-32. There were 39 deaths, 4 due to malignancy. Damon and Holub[3] in 1958 reviewed 209 cases of polycythemia. They reported 26 associated malignancies. Nine of these were renal carcinoma, 2 were cerebellar hemangioblastoma and one a middle-fossa meningioma. Because of the reported association of polycythemia with these particular lesions, they eliminated these cases from the series and reported 14 unrelated malignancies in 197 cases of polycythemia vera. The details of treatment and the time-relation of treatment to the development of the malignancy were not discussed.

TABLE 6.—PRIMARY MALIGNANCIES OCCURRING WITH POLYCYTHEMIA VERA

		Total Series			*Cause of death known*		
			Cases of cancer			*Cause of death cancer*	
		No. of patients	*no.*	*%*	*Deaths*	*no.*	*%*
No. P-32	Videbaek[26]	125	9	7.2	35	8	22.9
	Stroebel[24]	32	4	12.5	32	4	12.5
	TOTAL	157	13	8.3	67	12	17.9
P-32 treated	Stroebel[25]	241	4	1.6	39	4	10.2
	Lawrence and Donald	264	18	6.8	108	16	14.8
	TOTAL	505	22	4.4	147	20	13.6
Treatment unspecified	Damon *et al.*[3]	209	26	12.4			
TOTAL—All cases		871	61	7.0	214	32	15.0

In our own series of 264 cases of polycythemia vera 20 cases of malignancy including 2 cases of skin cancers, were found either at necropsy or at surgery. In 15 of 108 deaths, the malignancy was the cause of death. Two patients with malignancy diagnosed at surgery are still living. All of the patients in our series received radioactive isotopes. These various series are presented in Table 6. The apparent increase of cases of cancer found over those expected is even more striking

when only the deceased patients in each series are considered (Table 6), and this portion of the group may be more important in that the incidence of cancer is definite, while the living cases may yet develop malignancy. The incidence of cancer in the combined series of 67 patients not treated with isotopes is 17.9%, in the 147 treated patients is 13.6% and in the total 214 patients is 15.0%.

Table 7 shows the site of origin of the malignancies in the series reported by Stoebel, Videbaek, Damon *et al.*, and in our own series. The kidney shows an unexpectedly high incidence. This has been commented on in references 2, 4, 6 and 14. In our series there were 3 cases of carcinoma of the thyroid. In 2 cases this was an incidental necropsy finding occurring with a hypernephroma in one case and with a malignant melanoma in another. The third case diagnosed at surgery is still living, with her polycythemia vera requiring continued control one year after surgery. With the exception of the kidney and possibly the thyroid, there is no apparent predilection for any specific site.

As in the leukemia series, it is not possible to establish a control group

TABLE 7.—SITE OF PRIMARY MALIGNANCIES OCCURRING WITH POLYCYTHEMIA VERA

	Videbaek[2,6]	*Stoebel, Hall and Pease*[2,4]	*Damon and Holub*[3]	*Lawrence and Donald*	*TOTAL*
Skin or lips	1[a]		4	2	7
Gastrointestinal					
Esophagus	1[a]				1
Stomach		2	1	1	4
Colon or rectum	1		2	1	4
Pancreas				1	1
Respiratory—Lungs or bronchus	1		2		3
Urinary					
Kidney—hypernephroma	3	1	9	3[b]	16
Kidney—fibromyxoma				1	1
Bladder				1	1
Male—Prostate		1	1	1	3
Female					
Cervix uteri				1	1
Ovary				1	1
Breast	2		1	1	4
Thyroid				3[b,c]	3
Brain					
Fronto-parietal tumor			1		1
Meningioma			1		1
Hemangioblastoma, cerebellar			2		2
Glioblastoma				1	1
Malignant Melanoma	1			2[c]	3
Lymphosarcoma			1		1
Reticulum cell sarcoma			1	1	2
Hodgkin's			1		1
Multiple myeloma				1	1
TOTAL MALIGNANCIES	10	4	27	22	63
TOTAL PATIENTS	9	4	27	20	60

a. Carcinoma of esophagus and skin in one patient
b. Hypernephroma and carcinoma of thyroid in one patient
c. Malignant melanoma and carcinoma of thyroid in one patient

in the general population for a statistically valid comparison of the incidence of malignancy in polycythemia vera in the population at large. Our patients were all referred with the diagnosis of polycythemia vera established or strongly suspected. Also, the group was drawn from a very large geographical area, not only in the United States but throughout the world, with a preponderance, of course, from nearer areas. However, an estimate was made of the expected number of cancer deaths in a group of the same number of individuals in the general population surviving to the same 5-year age groups as the patients in our polycythemia vera series. This suggested that we could expect 4.8 cancer deaths in these 264 patients. We actually found 15 cancer deaths and a total of 18 cancer cases. Using the same method as in the leukemia series, we calculated the number of malignant neoplasms (excluding cancer of the skin) per 1000 patient-years observed as 11.03 in our series and the expected cancer deaths in the general population age groups covered by our average observation period as 4.96 deaths per 1000 patient-years (Table 3). These figures also are significant ($p = 0.001$).

The relation of radioisotope therapy to the production of malignancy must be considered in these cases. In Videbaek's series, which did not receive radioisotopes, the incidence of cancer was 7.2% in the entire group of 125 patients and 22.9% in the 35 deaths. In the series of Stroebel, Hall and Pease, also untreated with isotopes, the incidence was 12.5% of 32 deaths. The total of 67 cases not treated with radioisotopes yielded 12 cases of cancer or 17.9% of the deaths from cancer. The series of Stroebel and Law showed 1.6% incidence of cancer in the total of 241 cases and 10.2% incidence in the 39 deceased patients. Our own series shows 6.8% incidence in the total 264 cases and 14.8% incidence in 108 deceased patients. Thus the incidence in the 2 series of patients who received radioisotopes is 4.4% in 505 cases and the incidence in 147 deceased, treated patients is 13.6%. While the totals of patients in each group, treated and untreated, are not really comparable, there is no indication from these figures that radioisotope therapy has increased the incidence of cancer.

Discussion. While a review of the literature and of our series of cases points to an increase in primary unrelated malignancies with the chronic leukemias and with polycythemia vera, there is no indication of a reason for this increased association. In this regard the work of Gross[9,10] is of particular interest. By injecting newborn mice of a low-leukemia strain with cell-free extracts of organs from leukemic mice of another strain, he was able to produce leukemia in the injected mice. Many of the mice so injected, however, did not develop leukemia but did develop parotid tumors, or less frequently, subcutaneous sarcomas. This work has been reproduced by several investigators, among them Dulaney and others[5]. This suggests that there is a single virus capable of producing leukemia and at least 2 other types of malignancy in mice. Gross believes that such viruses or malignancy producing agents can be transmitted "vertically" by heredity to succeeding generations even frequently skipping generations in manifesting itself. As applied to humans, of course, this theory is highly speculative.

The relationship of polycythemia vera to leukemia has not been dealt with in this paper. Masouredis and Lawrence[19] in 1957 reported on the occurrence of leukemia with polycythemia vera in this clinic. This complication and its possible relation to radi-

ation therapy has concerned most investigators in this field (Lawrence[12,18], Stroebel, Hall and Pease[24], Stroebel and Law[25], Videbaek[26]) and deserves separate discussion.

Summary. A review of the literature and of our own series of cases of primary malignancy occurring in patients with chronic lymphatic leukemia, chronic myelogenous leukemia and polycythemia vera suggests that there is an increased incidence of cancer with these conditions. In the leukemias, there is no indication from the reported cases that there is a predilection for any specific organ or system. With polycythemia vera, however, there is a high incidence of renal malignancy (17 cases in 630 patients). Aside from this one organ there is no apparent close association. The role of radiation therapy in the production of the associated malignancies is not clear. In our own series and in other reported series of polycythemia vera patients there is no indication of an increase in malignancy in the radiation treated group as opposed to the group treated by other methods, but the number of patients is not large enough for adequate comparison. No series of untreated leukemias are available for analysis, but in our experience and in reports in the literature there is no indication that radiation in these patients has produced malignancy.

Our experience in agreement with the experience of others, then, indicates that patients with polycythemia vera and with chronic leukemia have an increased susceptibility to malignancy. This susceptibility is not produced by radiation therapy.

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SUMMARIO IN INTERLINGUA

Le Incidentia De Cancere In Patientes Con Leucemia Chronic O Polycythemia Ver

Un revista del litteratura e de nostre serie de casos personal de malignitate primari occurrente in patientes con chronic leucemia lymphatic, chronic leucemia myelogene, e polycythemia ver suggere que il ha un augmento del incidentia de cancere in le presentia del conditiones mentionate. Quanto al leucemias, le reportate casos non reflecte un predilection pro un organo o systema specific. Tamen, in polycythemia ver il ha un alte incidentia de malignitate renal (17 casos in 630 patientes). A parte iste organo specific, nulle intime association es apparente. Le rolo del therapia radiational in le production del associate malignitate non es clar. In nostre serie personal e in altere series reportate in le litteratura de casos de polycythemia ver, il non se nota un indication de un plus alte incidentia de malignitates in le gruppo de patientes irradiate in comparation con le gruppo tractate per altere methodos, sed le numero del patientes non suffice pro establir conclusiones significative. Nulle serie de nontractate casos de leucemia es disponibile pro le analyse, sed in nostre experientia e in le reportos in le litteratura il ha nulle indication que le radiation ha producite malignitates in iste patientes.

Assi nostre experientia—de accordo con le experientia de alteres—indica que patientes con polycythemia ver e con leucemia chronic se distingue per un augmentate susceptibilitate de disveloppar malignitates. Iste susceptibilitate non es le effecto de therapia radiational.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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MEDICOLEGAL OTOLARYNGOLOGY

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HEAD INJURIES. Many cases of head injuries have medicolegal aspects. Individuals who sustain head injuries may seek redress through common or compensation law. In rendering an award, the expenses associated with medical and hospital care and the degree of temporary or permanent disability measured in terms of earning capacity are assessed. In addition, judgments in common-law courts also include damages for factors not directly related to earning capacity, namely mental distress, pain, disfigurement, and personal grievances.

In a comprehensive, informative summary of the medicolegal aspects of head injuries, Walker[18] points out that the prime consideration of a physician when he interviews a patient with a head injury should be an accurate, detailed description of the accident, obtained from the patient as soon as possible after the occurrence of the injury and before the patient's befuddled memory is sharpened or distorted by accounts offered by friends or bystanders. If, for example, the accident was due to an automobile collision, it would be important to obtain information about the position of the patient in the automobile, his actual state at the time of the collision (asleep or awake, conversing or listening to the radio), the direction and speed of the automobiles involved in the collision, and the precise scene of the collision. According to Bickers[1], particular attention should be paid to alterations in consciousness resulting from the injury. Was the patient unaffected, dazed or unconscious? If unconsciousness is alleged to have occurred, the duration of retrograde and post-traumatic amnesia should be ascertained. In general, retrograde amnesia encompasses the mem-

ory loss for events taking place before the injury was sustained; post-traumatic amnesia, on the other hand, deals with occurrences from the moment of injury to the return of 'continuous remembering.' Although both states may not be present in severe head injuries, their occurrence and presence supplies an index of the severity of generalized disruption of cerebral function. In this connection, post-traumatic amnesia has been found to provide a better index of brain damage than retrograde amnesia. Retrograde amnesia may diminish or clear during recovery, but the duration of post-traumatic amnesia remains quite constant.

A fairly accurate assessment of damage to the brain depends not only on a history of an accident but also on data dealing with evidence of external violence, proof of impairment of mental functions, and neurological deficits or abnormalities. Evidence of actual injury to the head is supplied by a scalp laceration or bruise on the head. Sites of superficial trauma include the scalp and face, and are characterized by a black eye, bleeding from the ears or nose, or cerebrospinal rhinorrhea or otorrhea. These findings constitute prima-facie evidence of injury to the head. Impairment of consciousness immediately following an accident indicates that brain injury occurred. Declarations of impairment of consciousness are derived from testimony submitted by bystanders who observed the patient's behavior, or may be inferred by detailed inquiry into the patient's history. Little if any loss of consciousness and probably little brain damage ensues if a patient with a closed head injury is able to describe precisely what happened at the time of the accident, both before and after the actual moment of impact. Contrariwise, if the patient has a loss of memory for events preceding and following the accident, if only for a few minutes, it may be assumed that he had some impairment of consciousness. A consistent story by a patient that after sustaining the injury he became dizzy, had headaches, vomited, and experienced cephalic discomfort on moving is inferential evidence of some injury to the brain. Nonetheless, retention of consciousness is not absolute evidence that brain damage did not occur, especially in the case of open wounds of the head. The finding of some neurological abnormality (cranial nerve alterations, pupillary changes, transient differences in reflexes, or transient impairment of motor or sensory function of an extremity) shortly after a head injury has occurred indicates that the central nervous system has been affected.

A number of laboratory procedures afford objective evidence of injury to the brain or the head. Fractures visible in roentgenograms of the skull indicate that the head was subjected to at least a certain degree of violence. The severity of a head injury is not necessarily correlated with the extent of a skull fracture, insofar as severe neurological disturbances may follow injuries that cause very minor fissures in the skull, or no fractures whatever. In Bickers' opinion, roentgenographic examination during the acute stage of a head injury may sometimes be inadvisable; however, a single lateral portable film of the head and neck can be taken without dangerous manipulation of the patient in order to evaluate major cranial damage and to exclude associated injury to the cervical spine. Plain skull films can be taken at a later period, especially when medicolegal problems are anticipated.

Walker asserts that the cerebrospinal fluid may reveal the presence of blood when examined several hours after a head injury; this provides conclusive evidence of a head injury of some

magnitude, provided a ruptured aneurysm is ruled out. The presence of blood in the cerebrospinal fluid indicates laceration of vessels communicating with the subarachnoid space; the amount of blood found in cerebrospinal fluid is not the index of the severity of the sustained injury, for blood may be absent in the case of severe head injuries and present in relatively minor head injuries. An electroencephalogram taken shortly after a head injury may demonstrate alterations in the patterns of brain waves. As approximately 15% of the general population have some degree of electroencephalographic abnormality, the findings evinced by a single electroencephalogram should not be considered proof that the brain was injured, because it is difficult to conclude that a single electroencephalogram taken before the injury would not also have been abnormal. However, if repeated electroencephalograms of a patient who has sustained a head injury taken over a period of several weeks demonstrate reversal of the alterations of brain waves to a normal pattern, it is justifiable to conclude that damage to the brain produced the initial change in the electroencephalogram. Although of aid in locating intracranial hemorrhage, electroencephalography is less reliable than air studies and arteriography. In differentiating between functional disorders and epilepsy in post-traumatic states, especially in cases complicated by litigation or the desire for compensation, the electroencephalogram has proved helpful and at times decisive. A pneumoencephalogram may be able to establish the occurrence of damage to the brain by evincing alterations in the size and shape of the cerebral ventricles. Air studies may disclose generalized ventricular dilatation or distortion of one ventricle, the ventricle being pulled toward the damaged portion of the brain.

It is often mistakenly assumed that brain injury will lead to permanent mental or neurological impairment. Minor injuries and sometimes major injuries will frequently not cause the slightest demonstrable impairment of mental and nervous function. While it is probably true that a blow to the head which results in unconsciousness for more than an hour or two indicates organic damage to the brain that will be repaired by non-neural functioning tissue, it does not follow that such an injury will permanently impair cerebral function. In general, the ill effects of most head injuries pass off within 6 months; some patients, however, have persistent symptoms and neurological sequelae or paroxysmal attacks of unconsciousness to mar their return to good health.

Most patients whose head injuries are sufficient to impair consciousness experience symptoms of headache, dizziness, amnesia, mental confusion and nervousness for short periods of time, usually for a few weeks, although occasionally symptoms persist or recur for longer periods. In a small percentage of patients with persistent symptoms, these form such a consistent clinical pattern that they have been called the post-traumatic or post-concussional state or syndrome. This group of patients complains of headache, dizziness aggravated by postural changes, insomnia, tinnitus, difficulty in being able to concentrate, impairment of memory, visual disturbances, and anxiety. Whether the post-traumatic syndrome is due to organic brain damage or to neurosis has been a topic of controversy for generations. In evaluating the status of persons with this syndrome a year or two after injury, it is advisable to consider the findings of neurological examination, roentgenograms of the skull, electroencephalograms, psychometric testing (Wechsler-Bellevue, Minnesota Multiphasic Personality In-

ventory, and Rorschach), and, in some instances, psychiatric examination.

Follow-up studies of large numbers of patients with both open and closed head injuries have yielded several interesting observations. The post-traumatic syndrome occurs most often in persons who have by all available criteria sustained less severe types of head injuries and who have experienced either brief unconsciousness or none at all. Moreover, its incidence is greater in persons with personal inadequacies and correlates better with these factors than with the desire for compensation. Although financial settlements terminate many complaints, there are persons who are unaffected either by compensation or medical therapy.

Another major consequence of head injury is the fear of epilepsy or its actual development. About half of the number of head-injured patients in whom epilepsy develops will have had the first attack within 9 months after injury. Hence for practical purposes if a patient who has sustained a closed head injury has not evinced epileptic manifestations within 2 years, it is probable that seizures will not occur as a result of the injury. Furthermore, if the electroencephalographic findings are normal, it is reasonable to conclude that the patient is no more likely to have epileptic seizures than is any other normal person in the community. In open head injuries, after the second year and for the next 8 years, the chances for the development of epilepsy are about 1% per year.

In a discussion of the relationship of deafness to head injury, Guttman[7] asserts that impaired hearing may be present with or without gross physical evidence of injury to the bony skull, that head injury and skull fracture may produce a bilateral inner ear or nerve deafness, and that a basal skull fracture, not demonstrable by roentgenograms, may actually involve the temporal bone and produce deafness. Proctor, Gurdjian and Webster[13] have made a study of the physical factors present in fractures of the temporal bone. They point out that the petrous portion of the temporal bone forms two-thirds of the middle fossa and one-third of the floor of the posterior fossa and hence may be involved in fractures of the base of the skull. The fracture lines may extend toward the foramina of the petrosa as there are areas of stress concentration. Blows in the temporoparietal region spread the skull anteroposteriorly, causing vertical fractures in the lateral areas of the skull, which may extend to the base producing a longitudinal fracture of the temporal bone. Occipital and frontal trauma spreads the skull from side to side, fracturing it vertically near the midline. The fracture may extend to the petrous bone, causing a transverse fracture. According to these authors, they found 98 of 100 consecutive cases of head injuries showing signs or symptoms involving temporal bone structures. Lesions involving the external auditory canal were found in 8 out of 28 longitudinal fractures; tinnitus was noted in 36 cases; and deafness was found to be of the nerve type in 9 cases, and mixed in 13 cases. Vestibular disturbances were common, 50 patients complaining of vertigo.

OCCUPATIONAL DEAFNESS. Since we live in an age of noise and in an era of compensation, the medicolegal aspects of occupational deafness and acoustic trauma have assumed an importance which did not apply in days gone by. The prevention of occupational deafness in those who work in noisy surroundings is a task which otologists have to face, for both management and employees alike are vitally concerned, and both eagerly await an early solution.

The permanent hearing loss pro-

duced by extended exposure to certain occupational noises constitutes a serious health problem[5]. In an illuminating discussion of occupational deafness, Fox[2a,b,c,d] states that occupational deafness denotes hearing loss in one or both ears, partial or complete, arising during the course of, or as the result of traumatic injury, intense blasts or explosions, or gradually, as the result of prolonged exposure to hazardous noise levels. Direct trauma to the ear usually results from blows, foreign objects, and burns due to sparks and molten metal. The local trauma to the area may be followed by perforation of the tympanum and infection and often is associated with a hearing loss of the conductive or mixed type. These injuries are usually unilateral and tend to heal with appropriate management. According to Schuknecht and Davison[15], direct blows to the head can result in a hearing loss due to nerve damage, functional hearing tests revealing audiograms similar to those found in noise deafness.

The term acoustic trauma is frequently used to include industrial noise deafness as well as the sudden hearing loss produced by such loud noises as blasts, explosions and gunfire. In an address before the first Extraordinary Congress of the International Society of Audiology in 1954, Davis maintained that the two conditions would be better described by separate terms. He used the term acoustic trauma to mean the immediate injury produced by one or a few exposures to intense sounds, as illustrated by the hearing loss resulting from blasts or explosions. Industrial deafness, on the other hand, describes the loss of hearing that develops over a period of months or years of working in an environment of hazardous noise levels.

Noise has been defined as unwanted sound. It is the result of acoustic waves occurring at random frequencies and intensities. When the normal ear is exposed at damaging intensity levels for a sufficient time, a temporary depression of hearing ensues, which disappears after a period of rest. This temporary hearing loss is known as "temporary threshold shift." When ears are exposed for longer periods or to more intense sounds, the hearing loss becomes more severe and recovery is incomplete. That portion of hearing that never returns is referred to as noise deafness.

Many factors affect the degree and extent of hearing impairment found in cases of noise deafness. These are (1) intensity or loudness of the noise, (2) frequency spectrum of noise, (3) period of exposure, (4) individual susceptibility, (5) age of worker, (6) coexisting ear disease, (7) character of surroundings in which noise is produced, (8) distance from source, and (9) position of each ear with respect to sound waves. Of these, the four most important factors are (1) how loud the noise is (the sound-pressure level), (2) what type of noise it is (the frequency characteristics), (3) how long the period of exposure is (the duty-cycle per day and the length of total employment), and (4) how susceptible the worker is (whether he has so-called tin ears or tough ears).

The hearing loss resulting from noise deafness has certain characteristics. In the early stages of noise deafness the pure-tone audiogram is characterized by a sharply localized dip in the threshold curve between 3,000 and 4,000 cps. At this stage the subject is not aware of his loss and his only complaint may be due to tinnitus. As degeneration continues, the hearing for the still higher frequencies is affected and gradual involvement of the speech zone range occurs. The development of hearing loss is slow, and frequently the

worker is totally unaware of its existence and is apt to disregard it until he is quite deaf. The hearing loss in both ears is quite similar in extent and degree, and vestibular symptoms are rarely encountered. Local otological findings are usually normal. The pathology in cases of noise deafness encompasses involvement of the inner ear, resulting in disruption and degeneration of the hair cells of the organ of Corti with secondary degeneration of the ganglion cells.

House[9] states that the differential diagnosis of more advanced acoustic trauma after the patient has developed subjective deafness is more difficult. Pre-employment and routine periodic follow-up audiograms are essential to establish an accurate diagnosis, but it is more important to determine the presence of acoustic trauma at the earliest possible moment in order that protective measures may be instituted. In view of the insidious and slowly progressive nature of the lesion, Saltzman and Ersner[14] urge the necessity of active prophylactic measures by making working conditions more quiet and by the use of protectors in the ears of employees. Any worker showing audiometric evidence of acoustic trauma should be found employment in a less noisy industry.

Since industrial deafness is a compensable matter in a number of states, Nash[12] declares that the otologist should know what conditions are necessary for the establishment of a claim for occupational deafness and what conditions may cause its default, its disqualification and its deferment. In his opinion, the establishment of a claim for compensation arising from occupational deafness should be based on the following premises: (1) acoustic trauma, the result of an impact which is considered to be an accident, is not subject to the exceptions or stipulations imposed on industrial deafness which is adjudged as an occupational disease; (2) the noisy environment in which the claimant is alleged to have contracted occupational deafness must be conceded to be competent cause of such a disability, or evidence to support that assumption must be forthcoming; (3) the methods of determining the type and degree of hearing losses must be acceptable to the Workmen's Compensation Board or the Industrial Commission concerned; (4) the results of audiometric studies should compare favorably with the ability of the claimant to carry on a two-way conversation by means of spoken and whispered voice and should also compare favorably to the various tuning fork tests; repeated examinations should be a prerequisite of any claim and should produce results that are consistent and, therefore, acceptable though they may not necessarily be the same, for a hearing loss may progress or regress; (5) a proper interval after the claimant's removal from an environment of noise must be allowed in order to eliminate the element of acoustic fatigue and some of the other reversible elements already mentioned; (6) the amount or degree of any associated non-occupational losses of hearing in a case of total deafness must be appraised, as best they can be appraised and prorated as such; and (7) when all the aforementioned conditions have been fulfilled and the proper deductions made, the remaining deafness will be the permanent hearing impairment which comprises the element of occupational deafness with or without an element of presbycusis (the deafness of advancing age). In general, age is a factor which becomes of consequence when the worker is approaching 50 years at which time degenerative presbycusis is setting in. According to McLaurin[10],

presbycusis is assumed to produce a loss of at least 5% at 50 years of age, and of at least 10% at 60 years of age, even in persons with supposedly unimpaired function. He states that the question of age is likely to assume particular importance in those employees who postpone their claims for compensation until they reach retiring age.

The otologist who appears as a medical witness in cases involving noise deafness should be objective and scientific. Decisions as to when, how much, or under what conditions compensation is to be paid for loss of hearing are not for him to decide, but rather for the commissions and the courts. An otologist's statements should be based on reasonable medical opinions and conclusions and not on mere speculation. Some of the words that throw testimony into the category of speculation are "may," "could have been," "could be," "might," and "might have been." These are all terms of conjecture. As a rule, the opinions of the medical expert must be based not on medical certainty but rather on medical probability. Probability applies to that which is so reasonable or well evidenced that it almost induces belief. In other words, testimony should be based on what the expert would ordinarily expect to find in the usual circumstances.

Legislation dealing with occupational deafness has in recent years been enacted in Bulgaria, Czechoslovakia, Denmark, France, Germany, Soviet Russia, as well as the United States[17]. Although in this country all states have some form of workmen's compensation law, the provisions covering occupational hearing loss vary in the states and differ in interpretation even more. Most states afford the workman compensation in one form or another for loss of hearing caused by a sudden accidental event. The State of Wisconsin, which has been a leader in Workman's Compensation, passed specific legislation in 1955 dealing with hearing loss resulting from industrial noise exposure.

In this connection, a Medical Advisory Committee to the Wisconsin Industrial Commission had made a number of important recommendations. In brief, it was recommended that sound below 90 decibels, measured on a C scale of an approved sound-level meter, should not be considered harmful regardless of length of exposure. The sound-pressure level per octave band would determine the hazardous noise level. The inference to be drawn is that when there is noise above 90 decibels employers should be on their guard. For purposes of compensation, losses would be confined to those occurring for frequencies ordinarily used for speech conversation. Losses of hearing ability for tones above 2000 cycles per second would not be considered to constitute disability for hearing ordinary conversation. It was further recommended that the average hearing loss be defined by the sum of the losses at the three test frequencies divided by three. Pure tone air conduction audiometric tests were to be used for evaluating hearing acuity, using the readings of 500, 1000, and 2000 cycles per second. By means of a table the hearing loss would then be converted into percentage loss (Table 1).

Losses averaging 16 decibels or less would not constitute hearing disability, and losses of 80 decibels and over would constitute total deafness. To each average hearing loss between 17 and 79 decibels would be ascribed a percentage of compensable hearing loss. An average loss of 35 decibels corresponds to 30%, 47 decibels to 50%, 60 decibels to 71.7%, and 80 decibels to 100%. For binaural loss the ratio of hearing in one ear to loss in both ears

shall be considered to be 1:5. Loss due to presbycusis would be subtracted at the rate of 0.5% at age 50, and an additional 0.5% for each year thereafter. Since recovery of hearing may ordinarily be expected after removal from a noisy environment, and since the amount of recovery depends on years of exposure, degrees of loss and individual susceptibility, it was further recommended that a first examination be made after 48 hours' removal, followed by closely spaced periodic tests. To allow for the "recovery factor," 5

TABLE 1.—HEARING DISABILITY TABLE

Average Decibel Loss	*% of Compensable Hearing Loss*	*Average Decibel Loss*	*% of Compensable Hearing Loss*
17	.8	49	53.3
18	2.2	50	55
19	3.6	51	56.7
20	5	52	58.3
21	6.7	53	60
22	8.3	54	61.7
23	10	55	63.3
24	11.7	56	65
25	13.3	57	66.7
26	15	58	68.3
27	16.7	59	70
28	18.3	60	71.7
29	20	61	73.3
30	21.7	62	75
31	23.3	63	76.4
32	25	64	77.8
33	26.7	65	79.2
34	28.3	66	80.6
35	30	67	82
36	31.7	68	83.4
37	33.3	69	84.8
38	35	70	86.2
39	36.7	71	87.6
40	38.3	72	89
41	40	73	90.4
42	41.7	74	91.8
43	43.3	75	93.2
44	45	76	94.6
45	46.7	77	96
46	48.3	78	97.4
47	50	79	98.8
48	51.7	80 and over	100

Method—Add the pure tone air conduction losses in decibels for the three (3) frequencies 500, 1000 and 2000 c.p.s. and divide by three (3) to obtain average decibel loss. Find this average in the vertical column on the left (marked average decibel loss) and the percentage of compensable hearing loss for that ear is given directly opposite.

For Binaural Percentage of Hearing Loss use the following formula:

Four times the percentage of lesser loss;
Add the percentage of greater loss;
Divide total by five.

The resulting percentage is the loss of hearing in both ears and is applied to the schedule allowance for loss of hearing in both ears.

From Fox, M. S.: Laryngoscope, **67**, 1011, 1957.

decibels would be deducted from the average losses at the 500, 1000 and 2000 cycles. The result would be considered the final permanent loss, as of the time of examination so made, except for persons who had been removed from the noise for 6 months or longer, in which case the final determination could be made from actual readings. Any improvement by hearing aid would not be considered in the evaluation.

The new Wisconsin amendments pertaining to occupational hearing loss became effective on July 1, 1955. They defined occupational deafness and the industrial environment capable of producing the condition. A schedule was provided for partial as well as total hearing loss, allowing up to 32 weeks for compensation for total deafness of one ear and 160 weeks for total deafness of both ears. Employees could file claims for occupational loss of hearing 6 months after any of the following events provided they remained away from injurious noise for that length of time: (1) transfer because of occupational deafness to non-noisy environments; (2) retirement; (3) termination of employer-employee relationship; and (4) layoff for one year, the last 6 months of which is away from injurious noise. In one provision the Wisconsin Act states: "An employer will be liable for the entire occupational deafness to which his employment has contributed. However, if deafness previous to that which the employment has contributed is established by a hearing test or other competent evidence the employer shall not be liable for such previous loss." According to Fox, this emphasizes the need for pre-employment pure tone audiometric tests and consultation with otologists in supervising hearing conservation programs.

WHIPLASH INJURIES. In 1957, 40,000 Americans were killed in automobile accidents and 1,250,000 were injured. Fifteen per cent of those who sustained moderately severe injuries were involved in accidents in which a stationary automobile was struck from behind. The resultant force was responsible for whiplash injuries, a term which today is frequently used and abused. According to Frankel[3], whiplash injury of the neck is a term which describes what occurs in a particular accident wherein there is a forceful snapping backward of the cervical spine and a subsequent hyperflexion or a deceleration movement. The motion is comparable to the coiling and uncoiling of a snapped whip where the head is the weighted end of the whip. The mere fact that an automobile is struck from behind and a passenger is involved in a whiplash motion does not necessarily imply that injury will follow. Occasionally, when a passenger is braced, no injury results. When an automobile is struck from the side, a passenger may become the victim of a unilateral or oblique type of whiplash injury. Injuries to the cervical spine are responsible for many cases of litigation. Gelber[4] maintains that the medicolegal importance of whiplash injuries is becoming more apparent as time goes on. Although roentgenograms of the cervical spine may prove completely negative soon after an injury, a patient may nevertheless begin to complain of headache, dizziness, ocular symptoms, radiculitis, and neuromuscular pains in the hands and arms. From a medicolegal point of view, it is important to look for damage and complications involving ligaments and bones.

Seletz[16] believes that physicians should alter their basic concept of whiplash injury, for this is not alone a direct injury to bony architecture and soft muscle structures. While, occasionally, after whiplash injuries to the cervical spine, roentgenograms may re-

veal damage to bones and joints with possible dislocation or subluxation, the disabling and persistent symptomatology in most instances is due to involvement of delicate and vital nerves and blood vessels about the cervical spine. Pain and disturbed function are due to involvement of various cervical nerve roots, the spinal accessory nerve and the cervical autonomic nerve, including the vertebral nerve, and in the transient obstruction or compression of the vertebral artery. Many headaches can be attributed to traction injury of the second cervical nerve root, which is especially vulnerable to injury because it is not protected by pedicles and facets, as are all other nerve roots in the vertebral spine. Injury to the vertebral nerve produces spasm of the vertebral arteries and gives rise to disturbed circulation of the pons and portions of the medulla containing the nuclei of origin of the lower seven cranial nerves, with resultant far-flung symptoms.

In general, the symptoms of whiplash injuries may be divided into four categories: (1) cerebral concussion, (2) cervical radiculitis, (3) fractures of the cervical vertebrae, and (4) psychoneurosis. Clinical evidence of cerebral concussion is present in a fair number of patients, with symptoms varying from mental confusion or headache to loss of consciousness. In Frankel's experience, symptoms of cervical radiculitis were not associated with fractures in most cases. Patients complained of pain which radiated either to the occipital region or to the shoulders, arms and scapulae. Muscle spasm was a common concomitant finding. Various reflex changes occurred occasionally. Persistent radiculitis was believed due to edema and hemorrhage which occurred when there was an avulsion of the ligaments and tearing of some of the musculature of the neck. A predominance of fractures was noted in the area of the fifth and sixth cervical vertebrae, with the maximum compression force taking place above the fifth cervical vertebra. Psychoneurotic tendencies persisted for several months in a small number of patients, especially in those persons who were improperly immobilized.

Hawkes[8] declares that in whiplash injuries of the head and neck, roentgenograms are of great importance. In addition to conventional antero-posterior and lateral views of the cervical spine, right and left oblique views and films in the lateral projection with the neck flexed and extended are recommended. As a result of these studies, paraspinal hematomas, small fractures in which a fragment is pulled loose, and proper demonstration of muscle spasm are possible. The validity of interruptions of the normal curvature can be demonstrated by flexion and extension films, and if true muscle spasm exists, it should be reflected in all of these views. Roentgenograms should be made early in order that changes due to preexisting injury or disease can be recognized and established; at a later date it may be difficult to determine whether preexisting injury or disease were already in existence or were, on the other hand, the result of the injury under consideration. The question of aggravation of previous injury or disease may often pose a perplexing problem. On numerous occasions hypertrophic changes or narrowed disk spaces may be seen in roentgenograms made the same day of the injury in a patient who otherwise denies previous difficulties. Certainly, these changes may have occurred without symptoms prior to the injury and yet the effect of the injury would not have been the same had they not been present.

The possibility of whiplash injury to the lumbar spine is described by

Milch[11]. This entity is similar to that which occurs in the cervical and dorsal spines both as to appearance and etiology. Gotten[6] questioned 100 patients with previously diagnosed cervical neck strain incurred during automobile accidents and whose litigation on compensation claims had been settled as to their present clinical status. After legal claims for damage were completed, 88% of the patients evinced recovery, and more than half of these had no residual complaints. Many emotional factors, but especially those dealing with monetary compensation, greatly confuse proper medical evaluation and appear to be the cause of the wide divergence of professional prognostic opinions relating to whiplash injuries.

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DERMATOLOGY AND SYPHILOLOGY

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THE DERMATOLOGY OF CARDIOVASCULAR DISEASE*

A SURVEY OF SOME RECENT LITERATURE

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THERE are numerous cutaneous manifestations associated with diseases of the heart or blood vessels, or both. Silverman and Bernstein[109] selected a large group of cutaneous manifestations encountered in cardiovascular problems and emphasize that these processes indicate the importance of the visual sense in diagnosis (Table 1). Although Silverman and Bernstein[109] have performed a basic service, the reviewers feel that more extended search for simultaneous changes in the cardiovascular and cutaneous systems is in order. This report details such an effort. It must be noted that the association of cutaneous and cardiovascular lesions in a patient does not always mean relationship of the two processes. But, some occur together so often that the association cannot be attributed to chance. Occasionally the cutaneous counterpart may be the only indication of an underlying cardiovascular defect. Obviously, the range of subjects in this field is so large that details can be given only where they are most pertinent.

COLLAGEN DISEASE. *Lupus Erythematosus.* Before discussing the aspects of lupus erythematosus, it is necessary that the terminology of this disease be clarified. Discoid lupus erythematosus refers to the mucocutaneous eruption without systemic manifestations, whereas acute and subacute lupus erythematosus refer to the serious systemic invariably fatal types.

*Bean in his new book entitled "Vascular Spiders and Related Lesions of the Skin" discusses many of these problems (**Bean, W. B.:** Vascular Spiders and Related Lesions of the Skin. Springfield, Ill.: Charles C Thomas, 1958).

TABLE 1.—SOME ASSOCIATED CUTANEOUS AND CARDIOVASCULAR LESIONS[a,b,c]

Neurocirculatory Asthenia (Emotional)

Pale skin; tense muscles; wrinkled brow; beads of perspiration; excessive sweating of palms, soles and axillae; cold and cyanotic hands; tremors; tobacco-stained fingers and chewed-off fingernails.

Congenital Heart Disease

Accessary nipple; hemangioma; hare lip; spina bifida; polydactyly; syndactyly; arachnodactyly; cyanosis in the young[13]; Mongolism.

Patent Ductus Arteriosus with High Pressure in Pulmonary Artery

Cyanosis of lower extremities but not head and upper extremities.

Transposition of Great Vessels

Cyanosis intense over head and upper extremities.

Polycythemia (Proportional to Degree of Cyanosis)

Clubbing of "extremities" (fingers).

Patent Ductus Arteriosus with Reversal of Flow

Clubbing of toes and not the fingers.

Methemoglobinemia

Intense cyanosis in infants below age 6 months.

Arteriovenous Fistula

Triad: Cyanosis; clubbing of fingers and toes; polycythemia[123].

Osler-Rendu-Weber Disease (Hereditary Hemorrhagic Telangiectasia)

Multiple telangiectasia of skin and mucous membranes, commonly in hands, nail bed, lips and ears.

Marfan's Syndrome

Arachnodactyly.

Rhabdomyoma of Heart

Adenoma sebaceum and subungual and periungual fibromas of fingers and toes.

Bacterial Endocarditis

Osler's nodes; Janeway lesions; petechiae; clubbing of extremities in a noncyanotic patient with congenital heart disease. Peculiar muddy palor[35].

Ball Valve Thrombus Occluding Mitral Valve

Episodes of coldness, cyanosis and gangrene of fingers, toes, tip of the nose and ear lobe.

Hyperthyroidism

Smooth, satiny, flushed, warm and moist skin; Maron's sign; hyperpigmentation; Jellinek's sign; vitiligo; urticaria and angioneurotic edema; photosensitivity; excessive sweating of palms, soles and axillae; tremors of outstretched fingers; diffuse or circumscribed loss of hair; pretibial myxedema.

Myxedema

Dry, rough and cold skin; Eskimo face; sallow yellowish hue of skin; xanthoma in the skin; localized swellings in supraclavicular fossae and over dorsum of hands and feet; frequent moles; keratotic lesions of palms and soles; ichthyotic changes in lower extremities; ulcerations and infections that are slow in healing; coarse, dry, brittle hair; loss of hair of outer third of eyebrows; deformities and infections of nails.

TABLE 1.—SOME ASSOCIATED CUTANEOUS AND CARDIOVASCULAR LESIONS[a,b,c] *(Continued)*

Addison's Disease

Hyperpigmentation about knuckles, in lines of palms, over extensor surfaces of the body, pressure points, at anogenital region, the areola of breasts, and in scars. Hair also shows increased pigmentation, and yellowish discoloration of nails has been observed.

Acromegaly

Acromegalic facies; enlarged hands and feet; drumstick deformity of fingers; cutis verticis gyrata; thickened, flattened and grooved nails; abundance of freckles and moles; hypertrichosis.

Pheochromocytoma

Multiple neurofibromatosis (Recklinghausen's disease); hyperpigmentation; arachnodactyly-like fingers; vasomotor changes in skin of extremities during acute attacks.

Endocrine Hypertensive Syndrome (Cushing)

Buffalo hump; increase in fat about buttocks, thighs, thorax and upper arms; small appearance of forearms, feet and ankles; hirsutism; ecchymosis; acne.

Coronary Artery Disease

Cutaneous xanthoma; gouty tophi petechiae (**Gerlis, L. M.:** J. Clin. Path., **11,** 391, 1958).

Hemochromatosis

Bronzed pigmentation of skin.

Amyloid Infiltration of the Heart

Cutaneous amyloidosis; painful fissures and thickening of skin.

Porphyria

Patchy hyperpigmentation, sometimes surrounded by areas of vitiligo.

Ochronosis

Bluish discoloration of ear and nose cartilage; spotty pigmentation of facial skin.

Carcinoid Syndrome

Sudden flushing of skin, later mingling with patches of cyanosis and white blotches; initially diffuse reddening of face and neck, later spreading to trunk and extremities.

Liver Disorders Associated with Cardiovascular Repercussions

Jaundice; spider angiomas; palmar erythema; white nails; abdominal varices; petechiae, purpura and ecchymosis.

Uremia

Sickly yellowish color of skin; puffy eyelids; dry skin; purpura; urea frost.

General Nutritional Deficiencies

Profound emaciation; white cross striations in nails; stippling of nails.

Niacin Deficiency

Erythema, hyperpigmentation, atrophy of skin, and development of a "pellagrous glove."

Beriberi (Wet Type)

Edema.

Riboflavin Deficiency

Angular stomatitis with fissure formation in corner of mouth and lips; sharkskin appearance of skin around alar cartilages of nose, eyes, and occasionally over ears and malar eminences.

TABLE 1.—SOME ASSOCIATED CUTANEOUS AND CARDIOVASCULAR LESIONS[a,b,c] *(Continued)*

Vitamin A Deficiency

Dry, hyperkeratotic skin.

Vitamins C and K Deficiency

Hemorrhagic tendencies, petechiae and purpura.

Disseminated Lupus Erythematosus

Bright red macular eruption on exposed parts of face and bridge of nose and cheeks producing so-called typical butterfly lesion; erythematous rash on v-shaped exposed areas of neck and upper chest; scattered areas of telangiectasia; areas of macular hyperpigmentation; characteristic erythematous lesions on ends of fingers and toes, around nail beds, on thenar and hypothenar eminences, on soles and pads of feet; petechial hemorrhages and purpura on skin; joint deformities resembling rheumatoid arthritis; peripheral vascular manifestations of Raynaud's disease may be present.

Dermatomyositis

Dermatomyositis facies; skin of face may become colored; generalized edema; cutaneous eruptions of erythema multiforme or erythema nodosum.

Periarteritis Nodosa

Subcutaneous nodules; petechial hemorrhages; purpura; localized areas of skin necrosis; urticaria; erythema multiforme-like rashes; crops of painful nodules or papules on extremities and trunks which usually follow course of a superficial artery.

Scleroderma

Hard, waxy, pigmented wrinkleless appearance of skin; patchy atrophy and contraction of skin and subcutaneous tissues; masked facies; claw hand; Raynaud's disease; gangrene.

Scleredema Adultorum
(Bushke's Disease)

Diffuse nonpitting edema affecting face, neck and upper part of chest; hydrarthrosis.

Rheumatic Fever

Erythema marginatum; urticaria, petechiae, atypical forms of erythema multiforme; subcutaneous nodules.

Shoulder-Hand Syndrome

Trophic and vasomotor changes in hands. Skin of hands in early stage is pink or red—later, cyanotic or pale. Hand appears smooth, cold, and glassy. In advances stage: atrophy of bone, subcutaneous tissue, and musculature; contracture deformities resembling Dupuytren contraction.

Cor Pulmonale

Nodular skin eruption. Berylliosis.

Sarcoidosis

Small, firm nodules, sometimes brown or bluish in color, appearing over butterfly area of face, arms, and back and over interphalangeal joints of hands. Skin may be thickened from a diffuse infiltration of granulomatous process; Erythema nodosum.

Scarlet Fever

Acute erythematous rash followed by desquamation.

Diphtheria

Cutaneous involvement differentiated from "jungle rot."

Syphilis

Specific and nonspecific mucocutaneous lesions.

TABLE 1.—SOME ASSOCIATED CUTANEOUS AND CARDIOVASCULAR LESIONS[a,b,c] *(Continued)*

	Trichinosis
Edema of face and eyelids.	
	Acute Interstitial Myocarditis
Exfoliative dermatitis.	
	Anoxic Cardiac Damage
Cherry red appearance of skin (carbon monoxide poisoning).	
	Contusion of Heart or Pressure of Aneurysm of Arch of Aorta, or Both
Unusual type of cyanosis characterized by deep blue or bluish-black discoloration of face, neck, and upper part of chest (ecchymotic mask).	
	Cerebral Fat Embolism
Characteristic dark red, petechial eruption of skin and mucous membranes.	
	Dissecting Aneurysm of the Aorta
Ecchymosis of chest, abdomen, or lumbar area.	
	Superior Vena Caval Syndrome
Cyanosis and edema of face, neck, and upper extremities, accompanied by distended veins in these locations.	
	Peripheral Vascular Disorders
Pallor or rubor, signs of atrophy, sweat disturbances, evidence of infection, ulcerations, varicosities, and trophic changes in nails and hair.	
	Varicose Veins
Edema, pigmentation, eczema, scars, ulcerations and infections of lower extremities.	
	Raynaud's Syndrome
During an acute attack, fingers (sometimes toes, ears and tip of nose) take on waxy, cold pallor or cyanosis, later terminating in erythema. Gangrene or atrophic changes occur late.	
	Erythromelalgia
Diffuse, warm, reddening of extremities, resembling erysipelas.	
	Thromboangiitis Obliterans
Recurring migrating phlebitis.	
	Glomangioma
Solitary tumors beneath fingernails. Appear as tiny, bluish or reddish point and are characterized by exquisite pain and tenderness.	
	Aneurysms (Tracheal; Axillary; Innominate, or Subclavian) Cirsoid Aneurysm or Arteriovenous Fistula
Unilateral clubbing of involved extremities.	
	Hypertensive Disease
Distinctive ischemic leg ulcer. Ulcer is located superficially on lateral surface of ankle. Usually has purpuric base without typical inflammatory exudate. Ulcers may be extremely painful.	
	Sickle Cell Anemia
Ulcerations of legs, usually located over malleoli, chronic in nature, almost always infected; tall, lean habitus; atrophy of external genitals, and scanty facial hair.	

TABLE 1.—SOME ASSOCIATED CUTANEOUS AND CARDIOVASCULAR LESIONS[a,b,c] *(Continued)*

Heart Failure

Skin is cold (except in high output failure when it may be warm and flushed); superficial veins are engorged, and fingernail beds cyanotic; hyperpigmentation.

Pericardial Tamponade with Shock

Intense cyanosis of hands and feet.

Shock

Abrupt appearance of cold, cyanotic, moist skin during course of an illness.

[a]: Based on **Silverman, J. J., and Bernstein, A.:** J. Am. Med. Assn., **158,** 821, 1955.
[b]: Pain of herpes zoster should be differentiated from coronary pain.
[c]: Where only cutaneous process is mentioned, it is understood that cardiovascular lesions are also present.

Chronic discoid lupus erythematosus is characterized by well-defined plaques that involve the face, scalp, ears and lower lip. The lesions are chronic, progress slowly peripherally and demonstrate central clearing. The border of the lesions is sharply demarcated, elevated, erythematous and indurated. Their surface usually presents a dry, silvery, adherent scale which, when removed, shows characteristic keratotic plugs on its under surface. On the scalp, the disease results in localized areas of alopecia. Associated with these plaques are varying degrees of pigmentation and telangiectasia. The final result of the process is a superficial, stippled characteristic scar. It is now generally agreed that a certain percentage of the chronic cases may eventuate into the acute or subacute forms[58]. According to Marten and Blackburn[75], in one series 25% of 121 cases of subacute lupus erythematosus began as the chronic discoid form, while in another series approximately 20% of 62 cases of the acute form originally presented the chronic discoid type. In Marten and Blackburn's[75] series of 66 cases of chronic discoid lupus erythematosus, 50% showed some hematological abnormality, and it was their conclusion that clinically one was unable to determine whether or not hematological abnormalities would be found. Unfortunately, what the significance of these hematological changes indicated could not be assessed at this time. It would seem to us that those cases of chronic discoid lupus erythematosus that demonstrated hematological abnormalities should be considered as manifesting systemic changes and therefore should be classified as a systemic form. The eruption of the acute systemic type usually consists of bright red, edematous, coalescent patches which show little tendency to atrophy or scar formation. This eruption may involve any part of the body or mucous membranes but at some stage will be found over the butterfly area of the face and the v-area of the neck[92]. Erythematous, edematous lesions about the fingernails, nail beds, thenar and hypothenar eminences are characteristic. Purpura and alopecia are commonly found in acute systemic lupus erythematosus. In addition, mucous membrane lesions may be found and these are usually of an inflammatory and ulcerative character. According to Michelson[80], edema of the face and lower eyelids is a good indication of the severity of the process. Raynaud's phenomena is often an associated finding[54].

According to McCreight and Mont-

gomery[78], the same histologic changes are noted in all the types of lupus erythematosus. They studied 102 specimens from patients with systemic lupus erythematosus and 17 from patients with chronic discoid lupus erythematosus. An early lesion of chronic discoid lupus erythematosus may have the same appearance as a well-developed lesion from a patient with acute systemic lupus erythematosus. There was variation in the degree of changes, and this variation seemed to be dependent more on the age of the individual lesion than on the type of disease. It was apparent that no single pathologic change would allow a definite diagnosis of lupus erythematosus, but a combination of changes seemed to be relatively specific. These include hyperkeratosis, keratotic plugging, atrophy of the prickle cell layer, liquefaction degeneration of the basal cell layer, edema of the cutis, dilatation of the superficial capillary layers, a cellular infiltrate of lymphocytes distributed about the vessels and dermal appendages, the presence of a varying number of chromatophores laden with melanin and the absence of obliterative or proliferative changes in the walls of the deeper blood vessels. Along this line it is interesting to note that Shearn and Pirofsky[108] report that skin biopsies from 13 patients with cutaneous lesions revealed changes compatible with systemic lupus erythematosus in all. Biopsy specimens of skin from 2 patients without cutaneous lesions revealed normal skin.

From the dermatological standpoint, it is agreed that exposure to sunlight has in many cases triggered the onset of acute systemic lupus erythematosus[11]. How this effect is produced on the skin or its contents is as yet unknown, although it is universally recommended that these patients be protected from the rays of the sun.

Cardiovascular involvement occurs in a high proportion of cases of lupus erythematosus. Humphreys[47], however, in a study on the cardiac status of 21 patients who died of pneumonia complications of acute systemic lupus erythematosus, stated:

> ". . . it is obvious that it is often impossible to evaluate with any precision the severity of the cardiac lesions in the patient with acute lupus erythematosus. The patient dying of this disease often presents simultaneously, symptoms related to a polyserositis, including a pericarditis; to acute or chronic renal disease; to abnormalities of the nervous system; to nutritional disturbances; to chronic and acute pulmonary disease; to acute bacterial infections. At least a few of them have had preceding rheumatic heart disease. It is obvious why so little precise information can be obtained with the technics of physical diagnosis. Probably the best clue to the severity of cardiac injury is a series of electrocardiograms. Even this tool is subject to confusion, particularly in the presence of a pericardial effusion."

Libman and Sacks[67] described a type of endocarditis associated with white-centered petechiae, repeatedly negative blood cultures and the absence of Aschoff bodies in the myocardium. They considered this type of endocarditis to be distinct from bacterial or rheumatic endocarditis and named it "atypical verrucous endocarditis."

Shearn and Pirofsky[108] studied 34 patients with acute systemic lupus erythematosus and noted that 24 patients had systolic murmurs loudest at the apex. These murmurs were soft and blowing in quality. In 4 of these patients auscultation revealed a diastolic murmur at the cardiac apex, and at necropsy in 2 of these patients a Libman-Sacks type of endocarditis of the mitral valve was found. Congestive failure occurred frequently in this series and the heart was enlarged in 14 of the patients. Hypertension was found in 11 patients, gallop rhythm in 7, and a pericardial friction rub in 6.

Arryhthmias were rarely found and premature contractions were never found either clinically or by electrocardiogram. The changes in the electrocardiogram that have been described in systemic lupus erythematosus are prolongation of the P–R and Q–T intervals, low voltage, left axis deviation, and T wave abnormalities[68]. In their series Shearn and Piofsky[108] encountered flattening or inversion of the T waves as the most common abnormality and in no case was the P–R interval prolonged.

Gould and Daves[40] studied 100 cases of acute systemic lupus erythematosus, and calculated a 53% incidence of cardiac involvement. Roentgen-ray phenomena associated with cardiac decompensation were observed in 33 patients. There were 11 instances of pulmonary congestion and 8 cases of dilatation of the azygos vein, as well as 14 patients with edema of the soft tissues manifested by subcutaneous swelling and blurring of the cleavage planes. In 1958 Gould and Daves[41] attempted to determine the reasons for variable heart size which occur in patients with the systemic form of the disease. Definite Roentgen-ray evidence of myocarditis, pericarditis or endocarditis is rare in this disease, and diagnostic studies by the internist including electrocardiographic examination and even pericardiocentesis were unable to solve this problem. Finally, postmortem studies by the pathologist, although demonstrating inflammatory changes in the pericardium, endocardium and myocardium, could not justify the variability of heart size with the paucity of microscopic findings. Gould and Daves[41] concluded that:

"Nonetheless, with the exclusion of pericarditis and endocarditis as common causes of variability in heart size, there is no recourse but to implicate the myocardium in some way. Perhaps systemic lupus erythematosus produces a physiological impairment and elongation of the muscle fibers rather than gross morphologic and histologic changes."

Shaffer, James, Scully and Pillsbury[107], of the University of Pennsylvania, presented a case of acute systemic lupus erythematosus exhibiting severe widespread involvement of the cardiovascular system. This patient was a 27-year-old white woman with a classical eruption of acute systemic lupus erythematosus. In addition, she developed during the course of her illness areas of cutaneous gangrene which involved the digits, arms, legs, face and ear lobes. The lesions on the distal phalanges ended in gangrene and mummification. She also developed widespread purpura. At necropsy the following cardiovascular abnormalities were found: plastic pericarditis, endocarditis of the mitral valve and gangrene of the toes. Two additional patients with lupus erythematosus with cutaneous manifestations and vascular damage were reported by Shaffer, James, Scully and Pillsbury[107]. They concluded that there is a common pathologic denominator in lupus erythematosus and that this is vascular damage. The lesions demonstrating this principle, which were present in their patients, included a papulonecrotic tuberculid-like eruption, erythema nodosum, periarteritis nodosa, gross vascular occlusion, Raynaud's syndrome, diffuse swelling of the legs and gross gangrene of the skin.

Copeland, Capeller and Stern[19] reported on the clinical characteristics of 47 patients with systemic lupus erythematosus as well as the pathologic findings of 18. It is pertinent that 41 patients had cutaneous eruptions of one or more types, and that the classical characteristic butterfly eruption occurred in 29 patients. Twenty-eight patients showed areas of hyperpigmentation, while only 7 demonstrated cuta-

neous photosensitivity. This low incidence of photosensitivity in relation to the high incidence of hyperpigmentation may be explained by the fact that most of the patients in this series were Negroes. The heart was enlarged in about 50% of the cases. Ten presented a diastolic hypertension of 100 mg. of mercury or more. Evidence of heart failure occurred in 19 individuals. The high incidence of cardiovascular complications in this series may also be due to the known high incidence of hypertensive cardiovascular disease in American Negroes. Electrocardiograms were made on 39 patients. Fourteen were normal, and 10 revealed low voltage. Only 4 electrocardiograms showed changes compatible with pericarditis. An atrioventricular conduction defect was found in 4 patients, 2 of which were being treated with digitalis at the time the tracing was made. Eight patients presented nonspecific ST–T wave changes or P wave abnormalities.

Scleroderma. There are two types of scleroderma, the common feature of which is a leathery induration of the skin with a characteristic histologic appearance. Generalized scleroderma is a progressive disease of the connective tissue and the term as suggested by Goetz[38] of "progressive systemic sclerosis" adequately describes this form. It is recognized that some authorities make a distinction between scleroderma proper and systemic sclerosis including acrosclerosis, the latter being considered progressive vascular degenerative diseases[48a]. Circumscribed or localized scleroderma is a benign condition with no tendency toward generalized involvement. The cutaneous changes of progressive systemic sclerosis begin, as a rule, on the hands and feet and later spread to involve the face, neck and upper trunk. Generally three stages can be distinguished clinically: the edematous, the indurative and the atrophic. The mucous membranes may also be involved, especially of the mouth and pharynx, resulting in a shrinkage of the tissues of the gums, soft palate, uvula and the frenulum of the tongue. In addition, there is a frequent association of calcinosis in generalized scleroderma, and this is usually referred to as the Thibierge-Weissenbach syndrome[97,126]. The cardiovascular involvements in scleroderma were detailed by Beerman[8] in this Journal in 1948. To that date a considerable literature had accumulated. This indicated the extensive and frequent involvement of the cardiovascular system in this disease[8]. In a more recent survey by Piper and Helwig[87] of 31 patients with progressive systemic sclerosis, 17 exhibited Raynaud's phenomena. Of these 17 patients, 6 had signs and symptoms of Raynaud's phenomena prior to developing clinical signs of generalized scleroderma. In this series the most frequent symptom of progressive systemic sclerosis was referable to the joints, and second in frequency to joint symptoms as the initial manifestation was cutaneous involvement. Terminally, histologically, dermal lesions were found in 100% of the cases. In addition, it is surprising to note that cardiac lesions were found in 90% of the cases. The histological findings of the heart as recorded by Piper and Helwig[87] are as follows:

"Although many of the hearts did not weigh over 300 gm., a few weighed more than 400 gm. In general the degree of coronary arteriosclerosis was minimal. The outstanding change was fibrosis of the myocardium and this was present to some extent in 28 of the 31 hearts. The amount of fibrosis varied from small interstitial foci to large areas which replaced the myocardium. The fibrosis in turn ranged from a cellular fibroblastic type to a rather homogeneous fibrillar stroma with few cells. There was no apparent correlation between the degree of coronary sclerosis and the amount of fibrosis of the myocardium.

In many instances in the areas of fibrosis no change was observed in the blood vessels. However, in some there was intimal thickening and hyalinization. The pericardium occasionally exhibited fibrous plaques and in five hearts showed obliteration of the pericardial sac. There was no calcification."

Focal or diffuse fibrosis of the myocardium produces nonspecific changes in the electrocardiogram. Most of the nonspecific findings included T-wave inversion, prolongation of the QT interval, low voltage and various arrhythmias[10]. Escudero and McDevitt (Am. Heart J., 56, 6, 1958) also concluded from their study of the electrocardiogram of 60 patients with scleroderma that of all the mechanisms that may act in scleroderma, myocardial fibrosis is the most important. Roentgen-ray examination may reveal a peculiar triangular enlargement of the heart in scleroderma[131]. Certainly these findings are not diagnostic of scleroderma heart disease but do emphasize the profound systemic nature of this disease. Olson[84] stated that 38% of patients with generalized scleroderma develop malignant hypertension and that when this develops, the causes of death are similar to those of malignant hypertension. However, the cause of death in generalized scleroderma is usually due to intercurrent infection.

Dermatomyositis. Dermatomyositis is predominantly a disease of the skin and skeletal muscles, although it may affect many other organs. This process is best described as a nonsuppurative polymyositis with polymorphous cutaneous lesions. Two of 270 patients with dermatomyositis presented a pityriasis-rubra-pilaris-like cutaneous eruption[18]. The cutaneous changes in this disease are usually nonspecific. Ordinarily the eruption is erythematous and associated with brawny or soft edema. Vasomotor changes, especially Raynaud's phenomena, are frequently found and may constitute the earliest symptom. Other cutaneous changes include hyperhidrosis, alopecia, hyperpigmentation, telangiectasia, sclerodermatous changes and subcutaneous calcification. Hemorrhagic manifestations with purpura have been observed[53].

Wainger and Lever[128] reviewed the postmortem findings in 3 cases of dermatomyositis and observed the following changes in the cardiac muscle. In case 1 there was interstitial edema, and in case 2 there was interstitial edema associated with focal inflammation. Case 3 presented foci of mucoid degeneration of the interstitial connective tissue scattered throughout the myocardium, slight chronic inflammation between the muscle bundles and fibrosis of the endocardial connective tissue. It is interesting that in cases 1 and 2, although the histologic changes in the myocardium were mild, the electrocardiographic studies suggested generalized myocardial damage. It is possible that in dermatomyositis damage to the tissue may be more severe than the histologic findings indicate. Wakai, Brandenburg, and Kierland[129] studied the electrocardiographic findings in patients with polymyositis and dermatomyositis. They found that the electrocardiograms were normal in 70% of 27 patients. Electrocardiographic changes when present were nonspecific in nature. Low amplitude of the QRS complexes of the standard leads was the most frequent abnormality, and this was found in 5 of 27 patients. A common manifestation was tachycardia out of proportion to fever and this was found in 8 of the 27 patients. No arrhythmias or conduction disturbances were noted in any of these patients. Bacher[3] investigated the electrocardiographic changes in 102 cases of dermatomyositis. There were abnormalities in 33. Postmortem examination of the heart muscle in 3 cases revealed scat-

tered interstitial foci of round cells. From this it is apparent that all kinds of electrocardiographic changes may be found in this disease.

Cutaneous Lesions of Rheumatic Fever and Rheumatoid Arthritis. According to Campbell, Griffith, and Leake[15], more emphasis should be placed on the specific cutaneous changes that occur in acute rheumatic fever. It is their opinion that the eruption designated as erythema annulare rheumaticum in 1922 by Lehndorff and Leiner[65] is without doubt completely specific for rheumatic fever and is caused only by rheumatic fever. Urbach and Bleier[127] in 1940 emphasized the diagnostic importance of this specific cutaneous reaction. It was estimated by Lehndorff that 10% of the children with rheumatic fever will in the course of the disease present an eruption which most commonly involves the trunk and occasionally the arms and legs, but exempts the face[65]. The lesions are characteristically evanescent, and the pattern changes from hour to hour. They are a bright pink, flat and form circinate and gyrate patterns. Frequently the lesions first appear or become more prominent when the patient is undressed. The rings are usually 1 or 2 cm. in diameter, but may enlarge to 3 inches in diameter. In the florid cases, the lesions are sharply marginated and appear to be superficial. In the less pronounced cases, they are vaguely outlined and fade into a bluish cyanotic network that seems to lie beneath the skin surface. If the lesions are small and solid, they result in the not uncommon morbilliform pattern. The majority of the annular macular lesions remain unchanged at all times. Aside from its important specific diagnostic value, erythema annulare rheumaticum is also considered by some observers to be associated with cardiac damage. This opinion is not shared by all observers, and therefore, its validity is open to question. It is of note that in at least 50% of the cases this eruption appears subsequent to the joint symptoms. Often the eruption occurs as an isolated phenomenon, and its course is unrelated to other manifestations of the disease. As a rule the eruption is not influenced by salicylate therapy. It is the consensus that the eruption should be considered a sign of activity of the disease and handled as such.

Bates[4] studied 132 cases of acute rheumatic fever in young adults and found that the incidence of cutaneous manifestations was about 7%. He believes that the association of valvulitis and cutaneous manifestations is simply a matter of chance. Unfortunately, Bates[4] simply lists the cutaneous reaction as erythema marginatum, but does not describe its features. In addition, purpura occurred in about 4.5% of the reported cases. The purpura occurred most often at the acute onset of the attack and on the lower legs and ankles. The bleeding and clotting times are normal but the tourniquet test is usually positive. This indicates damage to the vascular network. Canizares[16a] also observed 233 cases of rheumatic fever in young adults. He found that cutaneous changes actually due to this disease could be detected in 10.3%. The dermatoses which he felt could be ascribed to rheumatic fever were urticaria, purpura, erythema nodosum, subcutaneous nodules, and erythema multiforme. Erythema multiforme occurred in eight patients (3.4%). Half of these had the papular type; the balance had ringed lesions which were classified as erythema annulare or erythema marginatum. He suggested the term "erythema multiforme rheumaticum (annular type)" for the group of processes called erythema annulare rheumaticum (flat type), and erythema

marginatum rheumaticum (elevated type). Canizares feels that erythema multiforme rheumaticum (annular type) is characteristic in its appearance, location and course. Its presence is strong evidence in favor of a diagnosis of rheumatic fever[16a].

The incidence of subcutaneous nodules occurring with acute rheumatic fever varies tremendously. Campbell, Griffith and Leake[15] report a 5.5% association, Still[119] reports a 27.5% association, Ingerman and Wilson[48] an 11% association and Keil[55] a 14% association. Subcutaneous nodules are small firm nodosities located most frequently about the elbows, and knees and less often scattered about other joints. Most patients have from 1 to 3 nodules but an occasional patient may have showers of 30 to 40 nodules. Most of these nodules disappear in a few weeks. Subcutaneous nodules are not specific for acute rheumatic fever since they have been observed in patients with syphilis, yaws, and rheumatoid arthritis; but when they are found associated with acute rheumatic fever, they have important prognostic implication. It is generally agreed that when they are present they indicate a severe type of infection with associated cardiac involvement.

Although it is well known that spider angiomata and palmar erythema occur in a variety of disease states as well as in physiological conditions, that is, chronic liver disease, pregnancy and aging, Bland, O'Brien and Bouchard[12] examined 152 patients with established rheumatoid arthritis and concluded that palmar erythema occurs in 61% of the patients while spider angiomata occur in 7.7%. This high incidence of palmar erythema should serve to make this an occasionally useful diagnostic physical sign of rheumatoid arthritis in obscure cases.

Periarteritis Nodosa. The term periarteritis nodosa introduced by Kussmaul and Maier[62] in 1866 is misleading, first because all coats of the vessel are involved and second because node formation is not an essential part of the disease. It is a widespread focal inflammatory disease of the smaller muscular type arteries. The process is recurrent and generally progressive. The lesions originate as foci of degeneration in the crotch of bifurcations and branching especially where medium sized arteries give rise to vessels of smaller caliber. Mature lesions are characterized by extensive fibrinoid necrosis and a pleomorphic inflammatory cell reaction but without foreign body giant cells. This process spreads throughout the wall of the vessel, and may result in thrombosis and small aneurysmal dilatations at the site of the lesions. According to Beerman and Mitchell[7], in true periarteritis nodosa the lesions are strictly arterial and involve the veins only by peripheral spread. Healing results in vascularized collagenized scars at the involved segments. The lesions may be seen in all stages and are widely distributed in the body, with the exception of the pulmonary circulation where they are not found unless pulmonary hypertension is present. The common clinical manifestations of periarteritis nodosa are polyneuritis, fever, and "multiple systems disease" and these effects can be attributed to stenosis or atresia of their blood vessels[135].

The clinical picture of this process, as would be expected, is extremely protean, but in general it must be considered in the differential diagnosis of fevers of unknown origin, especially with multiple organ system involvement[112]. The duration of the disease and its outcome are definitely related to the amount of involvement of the vital organs and the resultant functional impairment. Therefore, periarteritis nodosa need not result in death. Klein[60]

has reviewed the literature and presented 2 cases of periarteritis nodosa who recovered. From this study he stated that:

"Periarteritis nodosa is not invariably an acutely fatal disease. The course may be chronic with periods of remission and exacerbation. Recovery may occur. Recovery may be expected under the following circumstances: Confinement of the disease predominately to nonvital structures; minimal involvement of organs followed by healing, and localization of the disease to part of a single organ. Recovery can occur despite the involvement of vital structures, but death may follow in the inactive phase many years later from vascular insufficiency to such organs as the heart, kidneys or liver."

Further indication that the progress in periarteritis nodosa is not always grave is the experience of Slinger and Starck[111] who showed that in patients with a relatively mild course of the disease or when spontaneous remissions or complete recoveries were reported, cutaneous involvement seemed to be present. Ketron and Bernstein[57] found the incidence of cutaneous involvement in periarteritis nodosa to be around 25%. The following cutaneous changes have been reported: livedo racemosa, erythematous maculopapular lesions, hemorrhagic purpura and multiple ulcerations[60,111]. In suspicious cases, especially when there are no palpable nodules, a muscle biopsy should be performed and a careful histologic examination made of vessels in the removed tissue. A negative report, however, does not rule out the disease.

Allergic Cutaneous Vasculitis. Allergic cutaneous vasculitis is apparently what Gougerot[39,74] called nodular dermal allergide. It has received considerable attention lately, and Miescher[81] analyzed the whole problem under the title of "Vascular Allergid." He concluded that all forms may have a common allergic reaction mechanism, but further research is needed for a solid basis for classification. Zeek[135] made an acceptable classification of necrotizing angiitides on the basis of necropsy findings. The eruption developing on an allergic basis has a predilection for the lower extremities and consists of macular erythematous lesions and those suggestive of erythema multiforme or urticaria, in addition to the presence of nodules and purpuric macules. An occasional case may also present papillomatous lesions or bullae, or both. A single type of lesion may comprise the entire eruption or there may be a variety of combinations of the aforementioned lesions. Irgang[49] reports an illustrative case of allergic cutaneous vasculitis and registers a plea that more cases be reported. Histologically; the predominant abnormalities are mainly confined to the cutis and consist chiefly of a capillaritis and arteriolitis, fibrinoid necrosis of the perivascular tissue and a cellular infiltration composed largely of polymorphonuclear leukocytes, a number of which undergo degeneration[39,74,100]. Recently, Ruiter[98] introduced the term, "allergic cutaneous vasculitis" to describe a polymorphic eruption which histologically shows similar inflammatory process, but the predominating finding is an arteriolitis confined chiefly to the vessels of the cutis[43]. He felt that on pathological-anatomical grounds a classification could also be made for those forms of necrotizing angiitides which are chiefly confined to the skin. The histopathological changes demonstrated in this group of eruptions were, according to Ruiter[100], essentially the same although varying in detail in different cases. They consisted of inflammatory changes in the blood vessels, showing the histopathological picture of an allergic inflammation such as may be found, for example, in drug and infectious allergy. In evaluation of the clinical skin manifestations, a distinction is

made between disorders in which mainly the smaller (dermal) vessels are affected and those in which the medium-sized (subcutaneous) vessels are especially involved (the cutaneous type of periarteritis nodosa). The whole problem of "allergic" vasculitis is well presented by McCombs and his group[77a,77b].

Recently, a special form of vasculitis has aroused considerable interest, namely, *disseminated pathergic (allergic) granulomatosis (Wegener's granulomatosis)*. The classical clinical findings in disseminated pathergic granulomatosis are increasingly severe asthma, eosinophilia, recurrent bouts of pneumonia often simulating Loeffler's pneumonia, nonthrombocytopenic purpura and deep cutaneous and subcutaneous nodules. The findings in these cases are those of periarteritis nodosa, the commonest lesions involving the extravascular connective tissue of all parts of the body, most frequently the heart[69]. According to Winer, in the disseminated type of pathergic granulomatosis, the small vessels are involved and hyalinized. The focal type shows midface thrombosis and necrosis of the vessels. Pinkus felt that these lesions may be considered to be more chronic and show more proliferation tissue response to blood-borne allergens. In these cases, the early stage of the lesions is characterized by edema and leukocytes soon become necrotic; fibrinoid changes in the collagen set in, and a granulomatous reaction with histiocytes, sometimes in epithelioid arrangements and with numerous eosinophils develops. The most severe reaction of this type is seen in polyarteritis nodosa. A variant of disseminated pathergic granulomatosis designated malignant granuloma of the face may best be considered as an example of focal pathergic granulomatosis[118].

Nodular Vasculitis. Nodular vasculitis has been fully described by Beerman and Mitchell[7]. It is observed chiefly in middle-aged women and is commonly associated with hypertension[83]. The lesions are nodular and painful and characteristically involve the calves. Ulceration of the lesions is rare and generally they will clear with rest and elevation of the legs[7]. Irgang[50] reports 2 additional cases of nodular vasculitis associated with hypertension. Both were Negresses, one aged 57 with a blood pressure of 200/100, the other aged 41 with a blood pressure of 190/110. Since this disease occurs in middle-age or beyond, the hypertension may simply be a coincidental finding, but in view of the vascular abnormalities as observed histologically consisting of narrowing and thickening of the vascular walls, it is possible that the cutaneous lesions may represent local manifestations of a generalized vascular disease.

CHANGES IN THE SKIN DUE TO PERIPHERAL VASCULAR DISEASES. There is little doubt that the peripheral circulation shows dysfunction in certain dermatoses[46]. There are, however, certain peripheral vascular diseases which have secondary cutaneous components. Farber and Thayer[32] believe the proper identification of these cutaneous lesions favors early diagnosis and treatment. Although Farber and Thayer[32] have proposed an elaborate and detailed list of some peripheral vascular diseases which produce skin changes, many of them can be discussed under the headings: 1) trophic changes, 2) color changes and 3) changes in temperature.

1) Trophic changes result from ischemia. The cutaneous surface becomes dry, shiny, taut and atrophic. The hair, especially of the digits, is reduced or absent. Often the nails are brittle, rigid, opaque and distorted. Heavy calluses may form on the pressure points and seem to reflect the degree of local ischemia.

2) Color changes depend mainly

upon the amount and oxygenation of the blood flowing through the part. With decreased or absent arterial blood flow the part assumes a white color referred to as pallor. Rubor is a red color of the skin, the result of increased arteriolar flow, while cyanosis is a bluish hue due to slowed blood flow and increased oxygen withdrawal. In addition, there are pigment changes in the skin, usually of the lower extremities, and due mainly to chronic venous insufficiency with increased hydrostatic pressure resulting in diapedesis of red blood cells. The resulting color is due not only to the iron deposited in the cutis, but also to melanin production stimulated by the iron itself.

(3) Temperature changes depend upon the amount of flow through the part, impaired arteriolar circulation resulting in a lowering of the temperature, and an increased arteriolar circulation resulting in an increase in temperature of the part. An example of the former would be the cold limb of arteriosclerosis obliterans, and of the latter the increased temperature overlying an arteriovenous fistula.

It is necessary to keep these principles in mind in order fully to appreciate many of the entities to be described.

Relationship of Growth of Hair on Digits to the Severity of Ischemia. In a comprehensive study, Naide[82] was able to correlate the lack of hair growth on the toes with the severity of ischemia of the extremities. This is an important simple clinical sign because if there is enough blood to maintain the growth of hair in the toes, one can expect gangrenous lesions to heal. Conversely, if there is insufficient blood flow to maintain hair growth on the toes, necrotic lesions rarely heal and amputation is generally necessary.

Varieties of Digital Ischemia and Their Management. Edwards[23] has listed the causes of digital ischemia and has explained the pathophysiology in detail. The major causes are obstructive and vasospastic. Generally speaking, the effects of ischemia on the digits are the same regardless of the cause of the ischemia. The symptoms produced may be constant or intermittent, and may only be precipitated by decreases in environmental temperature. Tingling, numbness, pricking and burning pain sensations are common. Occasionally the nail plates may loosen and fall out. Finally, color changes may be observed. In longer standing cases, the ischemia results in atrophy of the digital pads. According to Edwards[23], certain signs suggest predominantly vasospastic diseases. He lists these as follows:

> "Ischemia, inconstant in degree; coldness without, or out of proportion to, major pulse loss; increased sweating of the hand or foot; thinning of the skin fold at the base of the nail, which merges into a widened cuticle, or pterygium (this has been observed in both Raynaud's disease and generalized scleroderma); tightness and loss of cutaneous markings and folds of the skin of the digits ('sclerodactyly') or of more of the limb ('acrosclerosis'); Roentgen-ray evidence of atrophy of the tufted ends of the terminal phalanges; and painful, puckered ulcers at the tips of the digits."

The Stasis Syndrome. Farber and Barnes[31] have discussed in detail the patho-physiology of the stasis syndrome. They compare the normal mechanisms responsible for venous return with the stasis syndrome. When varicosities begin, the hydrostatic pressure of the veins increases and accordingly fluid filtration into the tissues increases. This results in loss of protein and fluid by the capillaries into the tissue spaces. The loss is so large that the lymphatics are unable to reabsorb the unusually large amounts and edema results. The increased hydrostatic pressure in the capillary bed decreases the

capillary tone and either spontaneously, or as the result of minor trauma, erythrocytes enter the cutis where hemosiderin is deposited. Pigmentation results from the hemosiderin deposition as well as from increases in melanin formation. With persistent elevation of the venous pressure, the walls and valves of the lymphatic vessels become thickened and irreversible perilymphatic fibrosis develops. In addition, fibrous tissue proliferation is stimulated by edema fluid of high protein content. The involved area is periodically involved in a low grade inflammatory process and the final result is that of marked sclerosis. Occasionally calcium salts are deposited in the sclerotic areas. Ulceration and lymphedema are additional commonly known sequelae.

Thrombophlebitis Migrans. Lefemine and Warren[64] studied the course of thrombophlebitis migrans in 18 patients in an attempt to clarify the relationship of thrombophlebitis migrans to thromboangiitis obliterans and to establish a prognosis for patients with superficial thrombophlebitis migrans without evidence of arterial disease. Of the 18 patients with phlebitis migrans, 11 had signs of arterial occlusive disease compatible with thromboangiitis obliterans. The remaining 7 patients were free of arterial involvement at the time of initial examination. These 7 patients were followed from 3 to 11 years, and in spite of the continued activity of phlebitis migrans, no arterial disease developed in any of the patients.

Necrotic Lesions of the Leg in Arteriosclerosis. Edwards[24], in his discussion of necrotic lesions of the leg in arteriosclerosis, emphasized that necrosis of the skin and subcutaneous tissue can occur more proximally in the leg than the toes or feet. This necrosis may occur spontaneously as an infarction of the skin and subcutaneous tissues or it may follow local trauma or infections. Generally with an infarct as the cause, there is a sudden appearance of blue-red areas which quickly turn black. This is followed in a few days by sloughing and ulceration. These lesions are thought to be the result of thrombosis in small arteriosclerotic arteries. Small lesions of this type resemble those described by Hines and Farber[45] as "hypertensive-ischemic" ulcers. Necrosis following local injury or infection resembles that commonly seen in the toes, but the precipitating event, although mild, may initiate an advancing sclerosis.

Hypertensive Ulcer of the Leg. Hypertensive ulcer of the leg is an infrequent complication of hypertensive disease. The ulcer begins as a pigmented spot or reddish patch which soon becomes cyanotic. Shortly thereafter superficial ischemic necrosis develops, which, in turn, results in an ulcer with a greyish fundus. In many cases, the ulcer is bilaterally symmetrical and is located in the antero-exterior surface of the leg at the junction of the lower and median third. The ulcers are painful, and the pain is not relieved by bed rest. As a rule there are no visible circulatory changes or edema. According to Martorell[76], the diagnosis of an hypertensive supramalleolar ulcer should be based on the following:

"Considerable arterial hypertension in the arms.
Considerable arterial hypertension in the legs. Absence of main arterial occlusion in the extremities. Perceptible pulse in all arteries of the lower limbs.
Absence of disturbance of venous circulation. Existence of a superficial ulcer on the antero-exterior surface of the leg at the union of the lower and upper third.
Symmetry of the lesions; ulcers on both sides, or at least ulcers on one side and pigmented spots on the opposite side."

Blood Vessels of the Skin in Chronic Venous Insufficiency. Kulwin and Hines[61] inquired into the question of

the occurrence of pathologic changes in the blood vessels of the skin of the lower extremities of patients who had clinical evidence of chronic venous insufficiency. It was demonstrated that definite pathologic changes in the arterioles of the skin are a usual finding in areas of chronic venous insufficiency of the lower extremities, and that changes in the venules exist in approximately half the cases. The causal relation of these changes to the cutaneous manifestations, however, were not determined.

Livedo Reticularis and Summer Ulcerations. Feldaker, Hines and Kierland[33] describe idiopathic livedo reticularis associated with leg ulcers that occur during the summer months and heal during the winter months. This is in contradistinction to the usually occurring winter ulcerations. It is their contention that livedo reticularis associated with ulcers occurring during the summer months has not been a recognized syndrome. Histological studies revealed occlusive changes of the arterioles and veins which are similar to the vascular findings occurring in idiopathic livedo reticularis associated with winter ulcerations. The clinical picture is peculiar in that the livedo was worse during the winter when the ulcers would heal. Edema of the feet and ankles usually preceded the occurrence of the ulcers.

Keinig and Weber[56] studied the possibility that livedo reticularis was a variety of livedo racemosa. A survey of the literature shows that nearly all investigators identify livedo reticularis with cutis marmirata, or at least state that its pathogenetic mechanism is dependent on this. A correlation with livedo racemosa is refuted. This is regarded as a process with its own characteristics, based on a completely different etiology. The conditions under which cold can be expected to produce lesions are also discussed. Although frostbite shows its highest frequency in the cold season, it should, nonetheless, also be taken into account as a possibility during the spring and autumn and even during the summer itself. With this in mind, the so-called summer ulcerations are regarded as ulcerating perniosis in subjects of special disposition. The disposition results from various factors such as sex, peripheral asphyxia and cartilaginous edema, all of which are considered to be of hormonal and autonomic nervous origin. Similar conditions govern perniosis as it occurs in the wintertime.

Peripheral Vascular Failure as Cause of Death in Generalized Exfoliative Dermatitis. Steiner and Grayson[116] report 4 cases of generalized exfoliative dermatitis in which peripheral circulatory collapse was the cause of death. When this is contrasted with cardiac failure, peripheral circulatory collapse seems to be a rare cause of death in exfoliative dermatitis or in skin diseases in general. LeVan and Sternberg[66] listed as immediate causes of death in a review of 120 cases of skin diseases, bronchopneumonia, congestive failure, coronary accidents, uremia, lobar pneumonia, meningitis, the skin diseases *per se*, and "miscellaneous" conditions. With respect to generalized exfoliative drug dermatitis[89] and in cases of sudden death of eczematous infants[105], a collapse of the peripheral circulation seems frequently to be the immediate cause of the demise. In other fatal processes involving large cutaneous areas as in pemphigus and in most types of generalized exfoliative dermatitis except drug dermatitis, the literature has not incriminated peripheral circulatory collapse. Necropsy revealed abnormal changes in the adrenal cortex in 3 of Steiner and Grayson's[116] 4 cases. In 2 of them it was possible that the cortisone and corticotropin used in therapy were involved in the production of the fatal shock state.

The Hand and Cardiovascular Dis-

ease. According to Roesler[96], as well as Silverman and Littman[110], the size of the fist is a rough approximation of the area of the cardiac silhouette. Normally, the outline of the fist and the orthodiagraphic silhouette coincide, a small fist indicating a small heart and a large fist indicating a large heart. Degree of pallor can be assayed more accurately by observing the color of the palms than by noting the color of the oral mucous membranes or conjunctiva[133].

It should be noted that the hands are especially valuable for the study of the dynamics of the peripheral circulation. Generally, the color and temperature of the skin of the hands may yield more information of impending shock than either the pulse or blood pressure. If a warm, pale hand abruptly changes in appearance to a cold, deeply colored, cyanotic one, peripheral circulatory failure has indeed occurred[21].

In from 10% to 15% of cases of myocardial infarction, a perplexing and annoying entity, the shoulder-hand syndrome, occurs[22]. No relationship between the shoulder-hand syndrome and the type, location, or severity of the myocardial infarction could be ascertained. Steinbrocker[115] has listed three states in the evolution of the shoulder-hand syndrome:

"1. The first stages last from 3 to 6 months. The patient experiences pain, tenderness, and limitation of motion at the shoulder girdle followed by swelling, pain, stiffness, and discoloration of the hands and fingers. 2. The second lasts from 3 to 6 months. The shoulder pain and the hand swelling and discoloration gradually disappear, with stiffness and flexion deformity of the fingers becoming more prominent and manifestations similar to Dupuytren's contracture appearing. 3. The third lasts for months or becomes irreversible and is characterized by progressive atrophic changes in the hands, severe atrophy of the interosseus muscles, and limitation in motion at the metacarpophalangeal and interphalangeal joints."

According to Edeiken[22], the only treatment for the shoulder-hand syndrome is local heat, analgesics and a regimen of active use of the affected extremity. Of the 42 patients so treated by him, only 2 failed to recover. The prognosis is considered poor only in those patients with a "trigger" zone of sensitivity. It is recommended that patients with coronary occlusion be instructed to move their arms and shoulders while confined to bed and rest their head on their hands for 15 to 20 minutes 3 or 4 times daily.

VENOUS LAKES. Bean and Walsh[5] have described lesions which they have called "venous lakes." They are fairly common, benign and are found most commonly in elderly men who have lived an outdoor life. The localization of venous lakes is characteristic: about half occur on the ears and the remainder on the face, lips and neck. An individual lesion is small, about the size of a "simple blood blister," has an irregular elevated surface, and is of a purplish-blue color, deepest over the center and sometimes fading into a dark red color at the edge. Pressure on the lesion, either with the finger or by diascopy, expresses most of the blood. When pressure is released, a 1 to 2 mm. deep depression in the surface may be seen. Refilling of the lake occurs slowly, either from the center or from the small veins along the margin. Histologically the lakes have thin walls consisting usually of a single layer of endothelium with little supporting fibrous connective tissue. They have no muscle. Bean and Walsh[5] feel that the lesions are small varicose veins or varicules. It should be noted that this condition differs from nevi, cherry angioma, the venous star, the spider nevus, the caviar lesion and the telangiectasis of heredity hemorrhagic telangiectasia. The lakes are only of importance in differential diagnosis, and

knowledge of their benignancy allows the physician to reassure the patient.

GENERALIZED ANGIOMATOSIS. Madden[72] has classified the major group of generalized angiomatosis (telangiectasis), into the following subdivisions which he feels are distinctive:

"1. Primary Telangiectasia—This class can include hereditary hemorrhagic telangiectasia, certain cases of familial hematuria and epistaxis, not due to disease of the blood, in which no obvious telangiectasias have been seen; also familial cases of telangiectasia without hemorrhage, and certain possible examples of atavism without a family history.

"2. Secondary Telangiectasia—This group includes generalized telangiectasia dependent on constitutional diseases, such as disease of the liver and leukemia and angiomatosis occurring in pregnancy.

"All of the types of generalized telangiectasia under Becker's etiologic classification are included here: those of an infectious origin such as are seen in syphilis, those of endocrinous origin as seen in dysfunction of the endocrine glands, especially the thyroid and pituitary glands, those found in cardiovascular disease such as myocarditis, and the angiomatosis occurring in diseases affecting the nervous system, such as syphilis and lead poisoning.

"Lanceplaine's[63] three classes based on his pathologic-anatomic classification also are included in this subdivision: the neurogenous type presumably caused by damage to the vasomotor nerves, the mechanical type seen when an inflammatory process causes narrowing of the lumen of the vessel by endarteritis or compression caused by perivascular fibrosis, and the angiomatosis caused by toxic factors which are thought to destroy the strength of the wall of the vessel. Heredity plays no role in this type.

"3. Nevoid Telangiectasia—This type may be present at birth, it may appear early in life, or it may occur even in old age. Generalized, punctiform, capillary ectasias which occur in people beyond middle life and spider telangiectasias which appear at any age may be included in this subdivision."

Many authors[20,25,138] have expressed widely divergent opinions as to the cause of generalized angiomatosis, but it seems that both constitutional factors and precipitating factors must exist in cases of generalized angiomatosis. Telangiectasia is present in all types of angiomatosis but the number observed is not an indication of the extent in other organs of the body.

Hereditary hemorrhagic telangiectasia, which is by far the most important of the generalized angiomatoses, may be defined as an hereditary disease of the small blood vessels characterized by the formation of multiple, permanent localized dilatations. These may give rise to recurrent hemorrhages anywhere in the body, but usually in the form of recurrent epistaxis. The dilated vessels are most frequently noted in the skin of the face and in the oral and nasal mucosa. As a rule, these lesions are present at birth but become more obvious and more numerous as the individual gets older. The usual history is that of repeated small hemorrhage, but occasionally a single hemorrhage may result in death. If the source of the bleeding can be found, it is easily controlled by simple cautery. The prognosis must be guarded because a fatal hemorrhage may occur at any time from the various internal organs affected.

Garland and Anning[36] reviewed the literature as well as their own case histories to determine the genetic mechanism involved in hereditary hemorrhagic telangiectasia. On the whole, this defect appeared to be transmitted by men and women in approximately equal proportions. The age at which telangiectasia appeared varied greatly, but in most patients the lesions did not become conspicuous until after puberty. It is of interest that in some women the telangiectasia only became prominent during pregnancy. Garland and Anning[36] feel that this defect is probably more common than is generally realized. Epistaxis is the usual complaint and many patients are treated for this without the cause of their symp-

toms being appreciated. The consensus is that this defect is transmitted as a simple dominant trait.

ANGIOKERATOMA CORPORIS DIFFUSUM. Angiokeratoma corporis diffusum is a rare and unusual dermatosis characterized clinically by extensive, generalized, reddish, vascular papules containing a keratotic cap. This entity was first described by Fabry[30] in 1898. In general these distinctive cutaneous papules have their onset prior to puberty. Evidence has accumulated over the years so that it is now definitely established that associated systemic manifestations are an important part of the disease. As far as the cardiovascular manifestations are concerned, Ruiter[99,101,102] emphasized the associated hypertension and cardiac enlargement especially of the left ventricle. Fessas, Wintrobe and Cartwright[34], in a comprehensive survey, pointed out that organs other than the skin may be affected in this disease. They divided the cases into two categories, those with evidence suggesting systemic disease and those without information relative to the presence or absence of evidence suggestive of systemic disease. The cardiovascular findings included hypertension, cardiomegaly (clinically and roentgenographically demonstrable), electrocardiographic evidence of diffuse myocardial damage and cardiac insufficiency. Vascular changes (muscular) of the entire vascular system were found in tissues obtained from necropsy and biopsy specimens[90]. Increased amounts of glycogen were present in cardiac muscle, and chemical analysis of cardiac muscle showed, in one case, a 10-fold increase of the diaminophosphatides. Ruiter[99,101,102] described the deposition of a lipoid substance in all the vessels of the skin including even the capillaries.

Pittelkow, Kierland and Montgomery[88] have presented an additional case of angiokeratoma corporis diffusum in which the onset of the cutaneous lesions appeared prior to puberty, and there was occlusion of the vascular supply to the femoral capital epiphysis. In addition, this patient demonstrated signs and symptoms of cardiac involvement. On physical examination a Grade 1 apical systolic murmur was present, and the electrocardiogram revealed an intraventricular conduction defect. Although angiokeratoma corporis diffusum is a rare entity, it should be kept in mind that the cardiovascular system may be involved.

ENCEPHALOTRIGEMINAL ANGIOMATOSIS (STURGE-WEBER SYNDROME). Some recent literature on the Sturge-Weber syndrome was presented by Beerman[6]. The history of the process is briefly reviewed by Livingston[70] and his coworkers. They also reported 5 accurately studied cases. They also considered the problem of the pathogenesis of endocardial calcification. The absence, at postmortem examination, of phenomena of hemorrhage suggests that the calcium is not deposited in the localization of small hematoma.

Peterman[86] and others discuss the clinical picture of 35 cases of the Sturge-Weber disease. The characteristic picture is a venous angioma of the leptomeninges over the cerebral cortex usually associated with a port-wine nevus in the area of the skin supplied by the trigeminal nerve. The meningeal angioma and the port-wine nevus are located on the same side. Associated clinical abnormalities are focal or generalized convulsions, contralateral hemiplegia, and mental retardation, the result of cerebral cortical degeneration due to circulatory changes. In addition, angioma of the choroid and ipsilateral buphthalmos or glaucoma are often found. Roentgenographic findings are common and characteristic and are due to intracerebral

calcific or ferruginous deposits. The most common clinical feature found in 89% of the patients in this series was a convulsive disorder. Dermal venous angiomas were present in approximately 85%. Peterman's[86] group stressed variability of the clinical and diagnostic findings from patient to patient. They also note that in half the patients the course of the disease was not unfavorable. It is also pointed out that in those patients who do not respond to anticonvulsant medication, surgical excision of the cerebral cortex may offer a chance for recovery and prevent the progression of further neurological damage.

ACUTE VASCULAR PURPURA FOLLOWING IMMUNIZATION WITH ASIATIC INFLUENZA VACCINE. Stefanini[114] and others present a case of severe acute vascular purpura occurring a few days after an injection of polyvalent influenza vaccine. The patient presented a severe purpuric eruption that involved the buccal mucosa, tongue and major portions of the extremities. The patient was extremely ill but responded to intravenous infusions of adrenocorticotrophic hormone. It is interesting to note that antibodies were detected against the specific vaccine and not against the allantoic fluid content. They considered the patient's symptoms as a serum-sickness type of reaction to one of the constituents of the vaccine.

HEMOCHROMATOSIS AND THE HEART. Schreiber[104] has discussed hemochromatosis as a cause of cardiac failure and presents an illustrative case. Hemochromatosis causes a diffuse pigmentation of the skin which is indistinguishable from that seen in Addison's disease, but can easily be differentiated by histological examination. Although the reason for the cardiac failure in hemochromatosis is not yet settled, Swan and Dewar[121] are of the opinion that the extensive changes in the heart muscle, due to the iron deposition, is an adequate explanation. The case presented by Schreiber[104] had cardiac involvement with congestive failure. Electrocardiographic study demonstrated low voltage and S–T segment and T wave changes. During the course of this patient's illness, atrial fibrillation developed which responded to digitalis therapy. Histologically there was good correlation between the degree of myocardial fibrosis and the amount of hemosiderin deposition.

ACUTE PERICARDITIS AFTER SMALLPOX VACCINATION. Cangemi[16] details a case report of a 56-year-old man who developed acute pericarditis approximately 2 weeks after being vaccinated against smallpox. It is his hypothesis that pericarditis may result from an allergic reaction to the vaccine.

FUNGAL ENDOCARDITIS. In a recent comprehensive paper by Merchant[77] and others, 31 previously reported cases of fungal endocarditis are reviewed and 3 new cases were reported. The following types of fungi have caused endocarditis: candida, blastomyces, coccidioides, aspergillus, cryptococcus, histoplasma and mucor. Candida and histoplasma accounted for about two-thirds of the 34 cases. Clinically most of the cases resembled subacute bacterial endocarditis, and in these the endocarditis was an important manifestation of the disease. Aside from the obvious types of fungal endocarditis, Merchant[77] and his co-workers stress two clinical situations in which the diagnosis of fungal endocarditis should seriously be considered. One type is a patient with a known systemic fungal infection who has physical signs suggestive of endocarditis. Heart murmurs and evidence of major emboli are the two most important physical findings and should suggest endocardial involvement. The other type suggestive of fungal endocarditis would be a patient

with the clinical picture of subacute bacterial endocarditis in whom blood cultures are sterile and in which no obvious evidence of mycotic infection exists. In this type of case blood cultures for fungi should be performed as well as detailed examination of other organ systems.

SARCOIDOSIS OF THE HEART. Sarcoidosis is a systemic disease which may affect many organ systems. The cutaneous surface is frequently involved and the lesions are characteristic. They consist of soft, brownish-red intracutaneous papules, nodules or plaques which rarely ulcerate. Frequently central clearing occurs, resulting in annular patterns. These cutaneous changes show a tendency to symmetrical distribution and are usually of disseminated character, and characteristically the papules are found on the face, especially around the orbital and nasal regions. The most common forms of sarcoidosis are those in which pulmonary involvement occurs in combination with systemic lymphadenopathy. Others may present such involvement in association with lesions in various other organs, such as in the eyes, the lachrymal gland, the parotid glands, mucous membranes, spleen, and liver[51].

The heart may become involved in sarcoidosis either by direct invasion of sarcoid tissue or indirectly as a result of long standing extensive pulmonary changes[93]. There are many reports of primary cardiac involvement in sarcoidosis[37,53,91,117]. In a recent investigation, Peacock, Lippschutz and Lukas[85] reviewed the findings in 29 patients: 28 cases of sarcoidosis proved by necropsy and a case of sarcoidosis with the Stokes-Adams syndrome. Twenty-six had proven myocardial involvement and in 8 of these the pericardium was also affected. In 1 case the pericardium was involved and in the remaining 2 the epicardium alone was involved. In the patient with the Stokes-Adams attacks, the cardiac findings were those of cor pulmonale, and interestingly a section through the bundle of His revealed the endocardium and the underlying myocardium to be completely replaced by nodular tubercle-like lesions. In addition, sections through the interventricular septum showed sarcoid lesions in the endocardium and subendocardial musculature. Of course, the diagnosis of myocardial sarcoidosis has rarely been made during life, and when death is due to direct involvement of the myocardium, it will be associated with some arrhythmia including heart block.

KAPOSI'S SARCOMA WITH HEART INVOLVEMENNT. Kaposi's multiple idiopathic hemorrhagic sarcoma is a relatively rare but serious disorder. Visceral involvement occurs in about 10% of the patients suffering from this disease. While involvement of some viscera causes little or no clinical symptoms, serious difficulties occur when the heart, lungs or gastrointestinal tract are involved. Epstein[26] reviewed the reports of 28 cases of systemic Kaposi's sarcoma and found the heart to be the site of tumors in 5 instances. In all cases in which Roentgen-ray examination was made, a tumor in the right atrium with pericardial effusion was observed. Choisser and Ramsey[17] reported 2 instances of tumor occurring in the right atrium, causing a ball-valve type of obstruction at the tricuspid orifice and bringing about sudden death. Tumors may occur in any part of the heart in association with cutaneous manifestations and may cause pericarditis, effusion, heart block, arrhythmia or cardiac failure. Although there is some disagreement as to whether or not one can make a definite diagnosis of primary involvement of the heart by Kaposi's multiple idiopathic hemorrhagic sarcoma, Tedes-

chi[124] and his group are convinced that this does occur, especially in view of the systemic nature of this disease.

CARCINOID SYNDROME. Primary carcinoid tumors arise from Kultschitzky cells located in the crypts of Lieberkühn, and therefore may originate in any part of the gastrointestinal tract from the cardia to the anus[95]. The tumor cells secrete excessive quantities of 5-hydroxytryptamine into the blood stream[27,28], and this is thought to be responsible for most of the clinical manifestations of carcinoid syndrome. The prominent manifestations of the carcinoid syndrome involve four organ systems: (1) the skin, (2) the heart, (3) the gastrointestinal tract, and (4) the lungs. The most characteristic cutaneous sign is temporary paroxysmal cutaneous flushing, especially of the face. The flush is bright red or bluish-red with cyanotic patches throughout. In the more chronic types persistent cyanosis and telangiectasia develop. The flush reaction usually occurs spontaneously but may be precipitated by ingestion of irritants, emotions or mechanical stimulation of the tumor[59]. The tricuspid and pulmonary valves of the heart are affected by the carcinoid syndrome. These valves become vascularized, thickened, sclerotic and deformed. The sclerotic tissue may extend and form well-defined cushions overlying the intima of the pulmonary artery or the endocardium of the right atrium. It may extend to involve the thickened and fused cordae of the tricuspid valve. The final result of all these changes is that the tricuspid valve becomes stenotic or incompetent, the pulmonary valve funnel-like and stenotic. In general the mitral and aortic valves are not affected[44,79]. Although the cardiac changes are difficult to explain, it is interesting that according to Spain[113], some believe the cardiac changes could be the result of a nutritional deficiency, specifically of tryptophane, since large quantities of tryptophane have been found to be utilized by carcinoid tumors to form 5-hydroxytryptamine. Some observers note that in the South African Bantu the common occurrence of endocardial fibrosis is related to their low tryptophane diet. Confirmation of the clinical diagnosis can be made by detecting abnormal amounts of 5-hydroxy-3-indole acetic acid in the urine, and further confirmation of the diagnosis can be obtained by analysis of the tumor for serotonin[103].

PSEUDOXANTHOMA ELASTICUM. Pseudoxanthoma elasticum is a rare disorder consisting of minute, yellowish, round papules located on the sides of the neck, the shoulders, the axillae and occasionally on the abdomen and groins. The involved areas have the appearance of the skin of a plucked chicken. The affected skin is relaxed and often hangs in folds. The clinical characteristics of pseudoxanthoma elasticum can be grouped under three major headings, namely, cutaneous, ocular and vascular changes.

Szymanski and Caro[122], who reviewed the relationship of this disease to internal diseases, felt that it was a widespread disease of the elastic tissue[71,106]. Cardiac and vascular localization of this elastic tissue damage is believed to be responsible for the development of hypertension, cardiac decompensation, apoplexy, gastrointestinal hemorrhage, intermittent claudication and a number of internal medical complications. They also pointed out that Paget's disease of bone coexists with angioid streaks often enough to indicate they are manifestations of one disease. This concept has been concurred in by Shaffer, Copelan and Beerman[106] who also observed a patient exhibiting both diseases. They also presented an additional case with extensive peripheral vascular disease as-

sociated with gangrene of the lower extremities, widespread calcification of the major blood vessels and extensive calcinosis of the subcutaneous tissues.

The histopathological changes of pseudoxanthoma elasticum are diagnostic. Extending in a band across the midcorium are thickened, fragmented and curled elastic fibers, which stain purplish red with hematoxylin-eosin. There is very little change in the collagen and there is no merging of the collagen and elastic tissues. Fat and lipid stain are negative and xanthoma cells are not found. Cahill[14], Revell and Carey[94] as well as others had earlier called attention to the fact that pseudoxanthoma elasticum is a name given to the cutaneous lesions of a systemic disease of widespread disorder of the elastic tissue. Gronblad[42] and Strandberg[120] in 1929 remarked on the intimate association of pseudoxanthoma elasticum and angioid streaks of the retina. It is now an established fact that angioid streaks are produced by an alteration of elastic tissue of Bruch's membrane of the eye. Pathological changes in the vascular system manifests itself by a tendency to hemorrhage in one or more of many different organs. There may be intermittent claudication in the legs, coronary insufficiency, hypertension, premature calcification of peripheral arteries and hypertrophy of the left ventricle. Macroscopically whitish thickening of the endocardium of the atria and ventricules have been described, associated with similar changes on the pericardium. Histologically, degeneration of the elastic tissue has been demonstrated at these sites[14]. Hemorrhage from the gastrointestinal tract is one symptom that occurs with greater frequency than any other. In 1952 Wolff, Stokes and Schlesinger[134] presented the illustrative case of a 14-year-old boy who demonstrated many of the changes associated with pseudoxanthoma elasticum. The child had pseudoxanthoma elasticum associated with intermittent claudication since early childhood. He also demonstrated absence of pulsation in the distal arteries of the limbs, calcification in the proximal arteries, recurrent hemorrhages into the gastrointestinal tract, abnormalities in the fundi, and unexplained shortening of one tibia.

XANTHOMATOSIS AND CORONARY HEART DISEASE. Xanthomas are localized tumors in the skin. They are shiny, yellowish and vary in size from pinpoint papules to nodules several centimeters in diameter. There are three clinical types: (1) plane xanthomas located most frequently about the eyes where they are known as xanthelasmas, (2) tuberous xanthomas located about the extensor prominences, and (3) the papular xanthomas most commonly found on the buttocks, trunk and palms[29].

According to Beerman[9], although there are many bases for classification of the lipidoses (xanthomatoses), a reasonable classification of these disorders is given by Thannhauser and Magendantz[125]. From this classification it is noted that a very definite relationship exists between tuberous or plane xanthoma of the skin, xanthoma of the tendons and atheroma formation of the intima of blood vessels and of the endocardial lining of the heart. Beerman[9] emphasized that the diagnosis of the various lipidoses is a complex process and suggested that careful and detailed laboratory studies be performed before a definite opinion be rendered.

The occurrence of lipoidosis in families has been known for almost a hundred years. Recent interest in the hereditary (genetic) aspects of the xanthomatoses is indicated by the large number of publications on various aspects of the problem. Study of fam-

ily cases has added much in explanation of the less vital cutaneous lesions as well as the basis of coronary artery disease. The studies have disclosed a high incidence of associated cases (skin and heart). It would appear that the inherited defect is one of lipid metabolism (cholesterol)[1]. Xanthoma tuberosum, xanthelasma, angina pectoris, arcus senilis and atheroma are but variations or complications of the disease. The syndrome is not always complete in the affected members of a family, some individuals will show only hypercholesterolemia, arcus senilis and cutaneous lesions. Others may present occlusive arterial disease of the lower extremities associated with hyperlipemia and xanthoma tuberosum. Wilkinson, Hand and Fliegelman[132] presented a study involving four generations composed of 159 of 282 individuals available for detailed investigation. They found 30 persons with elevated blood cholesterol values. Five of these suffered from xanthoma tuberosum or xanthelasma, 1 from angina pectoris, 2 from xanthomatous valvular heart disease, 12 demonstrated a probable gallbladder disease and 5 had hepatosplenomegaly. In the group with normal blood cholesterol, there was one instance of xanthelasma, 1 of arcus senilis, 1 of angina pectoris, 12 of proven or suspected gallbladder disease, and 3 of hepatomegaly. Alvord[2] in 1949 reviewed the literature on this subject and presented the interesting family history in which 15 members had hyperlipemia, 6 had xanthoma tuberosum, and 18 a history suggestive of coronary artery disease. From his study and review of the literature, he concluded that in xanthomas:

(1) "a disturbance of lipid metabolism was the basic inherited defect, and (2) hyperlipemia (hypercholesterolemia) was inherited as a simple autosomal dominant trait."

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PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF JANUARY 20, 1959

SEMINAR ON ALKALOSIS

The Chemical Environment of the Respiratory Center. EUGENE D. ROBINS, M.D. (Department of Medicine, Harvard Medical School and the Medical Clinics of the Peter Bent Brigham Hospital). Previous studies on the chemical control of ventilation have assumed that the acid-base changes of extracellular fluid parallel the acid-base changes of the respiratory center. A study of the acid-base characteristics of spinal fluid reveals the fact that this compartment is freely permeable to CO_2 but relatively impermeable to bicarbonate ion. Numerous studies have shown that when the kinetics of a given substance differ between brain and extracellular fluid the kinetics in spinal fluid resemble those in brain and not blood. Evidence also indicates that most cells, with the exception of erythrocytes, are relatively impermeable to bicarbonate ion. It, therefore, appears likely that acid-base changes in spinal fluid parallel intracellular acid-base changes. Physiologically, the major substance which modifies intracellular pH is CO_2. On the assumption that acid-base changes in spinal fluid mirror brain intracellular changes, the initial step that causes increased respiratory center activity appears to be an increase in respiratory center CO_2 tension with a resultant fall in pH. But hyperventilation continues even when CO_2 tension drops below resting levels and pH rises above resting levels. It appears unlikely that either CO_2 or pH constitutes the ultimate chemical stimulus to ventilation.

Comparison of the Influences of Sodium Lactate and Meperidine Upon Blood Acid-Base Parameters and Their Relationship to Respiration in Man. S. J. G. SEMPLE, M.D., C. J. LAMBERTSEN, M.D., M. G. SMYTH, M.D., and R. GELFAND (Laboratory of Pharmacology, University of Pennsylvania School of Medicine). As previously reported, an intramuscular dose of 150 mg. meperidine produces a decrease in the threshold and sensitivity of the respiratory response of normal men to carbon dioxide. The meperidine-induced fall of ventilation was small while breathing air but because of the loss of sensitivity to CO_2 the depression of ventilation was relatively greater when respiration had been stimulated by CO_2 administration. In 6 normal male subjects breathing air, a similar "threshold" depression was observed after intravenous sodium lactate (2.4 mEq. per L.). However CO_2 administration did not enhance this effect, CO_2 sensitivity remaining unchanged.

Interpretation of the relationships among these results is handicapped by lack of certainty regarding the primary chemical stimulus to respiration. During CO_2 breathing, blood cH, pCO_2 and bicarbonate are all increased. Associated with respiratory depression following meperidine and sodium lactate, pCO_2 rises. However blood cH

rises after meperidine and falls following lactate.

In a separate series of experiments, an attempt was made to separate the respiratory effects of changes in blood cH and pCO_2. The latter was monitored at each breath and a desired level maintained constant through use of a gas ratiometer to vary the CO_2 inhaled. End-tidal pCO_2 was controlled in this way in 5 normal male subjects at 44.4 mm. Hg (S.D. ± 1.1) and 50.7 mm. Hg (S.D. ± 0.7) and the respiratory minute volume (R.M.V.) measured. The corresponding arterial blood values were 44.6 mm. Hg (S.D. ± 1.6) and 50.3 mm. Hg (S.D. ± 1.6). Twenty to 40 minutes after injection of sodium bicarbonate intravenously (2.4 mEq. per L.), RMV was measured, with end-tidal pCO_2 again controlled at 50 mm. Hg. Forty per cent of the original increase in ventilation produced by raising end-tidal pCO_2 from 44 to 50 mm. Hg was abolished by use of sodium bicarbonate to eliminate the increase of blood cH normally associated with the rise in pCO_2. Possible explanations for the remaining 60% of the ventilatory increase include: (a) That CO_2 has a specific effect independent of its ability to acidify blood and tissues; (b) that the chemical control of ventilation is determined entirely by cH, but that changes observed in blood do not accurately reflect the cH at the site of stimulation. Pertinent to the second possibility is the slow rate of transfer of intravenously injected bicarbonate into C.S.F. Under the circumstances of the present study, C.S.F. cH should be determined largely by its pCO_2.* Calculation of C.S.F. cH from values for arterial plasma bicarbonate during air breathing and internal values for arterial plasma bicarbonate during air breathing and internal jugular pCO_2 suggests that at 50 mm. Hg arterial pCO_2, injection of bicarbonate, while it lowered arterial cH, did not diminish C.S.F. cH. Changes in the cH of C.S.F. have considerable influence upon ventilation. Thus, on administration of bicarbonate, the effective cH at the respiratory centers of our subjects may have been determined by a compromise between the acid cH of C.S.F. and the induced alkaline shift of blood cH. When ventilation was compared with the simple mean of arterial and C.S.F. cH, changes in ventilation were found to have a precise relationship to cH both before and after bicarbonate injection and to lack correlation with changes in pCO_2.

Renal Chloride Conservation as Related to the Metabolic Alkalosis of Potassium Depletion. E. J. Huth, M.D. (Department of Medicine, School of Medicine, University of Pennsylvania). Experimental potassium depletion in rats has suggested that chloride loss in urine or stool is increased by potassium deficit and contributes to the alkalosis seen in this depletion.

To examine this question in man, a healthy male was depleted of potassium by use of an alkaline synthetic diet low in potassium (7 mEq. per day) and chloride (3 mEq. per day). For control, he later ingested a similar diet with a potassium content of 114 mEq. per day for 17 days.

The highly alkaline diet led to greater loss of urinary potassium than in a previous depletion in this subject using a $Cl:HCO_3$ dietary ratio of 3:1. The potassium balance (corrected for nitrogen balance) was —408 mEq. with the low potassium intake and —233 in the control study. Final venous serum potassium and total CO_2 values

*Robin, E. D., Whaley, R. D., Crump, C. H., Bickelmann, A. G., and Travis, D. M.: J. Appl. Physiol., 13, 385, 1958.

in the low potassium study were 3.0 mEq. per L. and 38.4 mM. per L. and 3.7 and 30.6 in the control study.

Stool chloride loss was negligible (<0.5 mEq. per day); there was no increase as the potassium deficit increased. The chloride balance showed a deficit in the low potassium study 50 mEq. greater than in the control study during the same interval. This additional chloride deficit was accounted for partly by lower chloride intake in the depletion study (3 mEq. per day against 8.0 in the control study) but more by greater urinary chloride losses in the first 3 days of potassium deprivation. As the potassium deficit increased, chloride conservation improved and was fully effective in the last 6 days.

The additional chloride deficit could account for the rise in serum bicarbonate in the potassium depletion study above that in the control, except for the fact that the changes in these two parameters were separated by an interval of one week.

SUMMARIO IN INTERLINGUA

(See page 418 for original article)

Le Mobilisation De Lipido In Consequentia Del Stress De Interventiones Chirurgic

Le effecto del stress de interventiones chirurgic super le concentration del hormon de mobilisation de lipido in le plasma e super le lipidos del plasma esseva investigate in 26 patientes.

Essayage de hormon de mobilisation de lipido, determinationes de cholesterol e de acido grasse, e registration de electrophorese a papiro del lipoproteinas esseva effectuate con specimens de sanguine obtenite ab le vena antecubital ante e 4 horas post le intervention chirurgic. Simile tests esseva effectuate con specimens obtenite ab le arteria omental e ab le vena omental al comenciamento e al fin de operationes intra-abdominal.

Le plus importante constatationes e lor signification pare esser:

(1) Esseva obtenite indicios que hormon de mobilisation de lipido es emanate sub stresses chirurgic; (2) isto resulta in le mobilisation de triglyceridos ab le reserva omental; (3) il occurre un marcate displaciamento in le electrophorogrammas a papiro ab predominantia de lipoproteina alpha verso predominantia de lipoproteina beta in le vena omental durante un operation chirurgic; (4) le omento non solmente responde activemente al presentia de endogene hormon de mobilisation de lipido per un effluxo del supra-mentionate componentes lipidic, illo etiam pare remover cholesterol ab le sanguine que circula a transverso illo; e (5) le alterationes de lipido que pote occurrer in le sanguine peripheric durante stresses chirurgic reflecte le mentionate eventos si ben como le capacitate del hepate de metabolisar le lipidos que es presentate a illo.

Es concludite que iste observationes in patientes suffrente le stress de interventiones chirurgic permitte le delineation de un mechanismo physiologic in humanos le qual es responsabile pro le mobilisation acute de lipidos verso le hepate.

BOOK REVIEWS AND NOTICES

NORMALE UND PATHOLOGISCHE ENTWICKLUNG DES MENSCHLICHEN HERZENS. By KLAUS GOERTTLER, Department of Pathology, University of Kiel. Pp. 123; 54 ills. Stuttgart: G. Thieme, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $7.85.

THE study is based upon the analysis of 21 malformed hearts. The dynamics of the embryonic development of the heart is presented. The formal cause for malformations is an arrest of growth of segments of the myocardial tube, at different time periods, brought about by endogenous or exogenous factors. Types of malformation are correlated with age and length of embryo, as shown in Table 3. Due credit is given to the pioneer work of Spitzer. The anomalies of the great arteries and veins in the chest cavity are given in detail. There are 137 references. Photographs of specimens and schematic drawings are of superior quality. To fully appreciate the significance of this monograph, a good knowledge of cardiac embryology is a prerequisite.

H.R.

CHRONIC ILLNESS IN THE UNITED STATES. VOL. IV. CHRONIC ILLNESS IN A LARGE CITY. THE BALTIMORE STUDY. By the COMMISSION ON CHRONIC ILLNESS. Pp. 620. Cambridge, Mass: Harvard University Press for The Commonwealth Fund. Price, $8.00.

THE Commission on Chronic Illness was a voluntary national agency which was founded jointly by the American Hospital Association, the American Medical Association, the American Public Health Association and the American Public Welfare Association. It functioned from June, 1949, to June, 1956. Its purpose was the study of the problems of chronic disease, illness and disability. Its work was supported largely by the United States Public Health Service through research grants and by the Commonwealth Fund, with some assistance from the Eli Lilly Company. Its findings are being published in four volumes: Volume I, on the Prevention of Chronic Illness, and Volume II, on the Care of the Long-Term Patient, have appeared and Volume III, on Chronic Illness in Rural Areas is due soon to appear. Volume IV the final one of the series deals with Chronic Illness in a Large City. With the cooperation of the staff of the Johns Hopkins University and Hospital a sample population group was examined in the City of Baltimore to get data on the amount and kind of chronic disease existing in the general population. Part I of the volume reviews efforts to study the size and scope of the chronic illness problem and describes the plan and methodology of the Baltimore survey. Parts II and III respectively deal with the volume and character of chronic disease and the needs for care and rehabilitation. Part IV gives the results of screen tests for detecting certain diseases and discusses the physiological characteristics of the population group observed. Part V gives data on disability as reported in household interviews. Part VI, in the light of the experience garnered in the present survey, suggests methods of studying chronic disease in the general population. This section should prove most helpful for those planning future studies. The whole series and particularly Volume IV represent a valuable contribution to the literature in the field of public health. R.K.

THE PHYSIOLOGY AND PATHOLOGY OF THE CEREBELLUM. By ROBERT S. DOW, M.D., PH.D., Associate Clinical Professor of Medicine (Neurology), University of Oregon Medical School AND GIUSEPPE MORUZZI, M.D., Professor and Head of the Institute of Physiology, University of Pisa, Italy. Pp. 675; 182 ills. Minneapolis: University of Minnesota Press, 1958. Price, $12.50.

THE authors, an American Clinical Neurologist and an Italian Neurophysiologist, have collaborated to provide a comprehensive review of cerebellar physiology and a survey of the clinical symptomatology and pathology of cerebellar disorders.

The authors have applied the recent development of electrical methods of recording activity in the nervous system to facts derived from older methods of investigation. They have also included previously unpublished reports of experiments conducted at the Institute of Physiology, University of Pisa, Italy.

Part I of the treatise deals with Physiology. There are also chapters on the history of cerebellar physiology, ablation, stimulation, and electro-physiological experiments. The relations between the cerebellum and other

central nervous structures, developmental physiology, and the functions of the cerebellum are considered in the remaining chapters in this section.

Part II deals with diseases of the cerebellum in the human. This section includes chapters on convulsive and hyperkinetic disorders, developmental anomaly, acute inflammatory and toxic disorders, chronic infections, cerebellar abscess, vascular disease, cerebellar trauma, and cerebellar tumors.

A very extensive bibliographical index completes the volume.

This volume should be of interest to the neurophysiologist, neurologist and neurosurgeon. M.S.

CURRENT THERAPY, 1958. Edited by HOWARD F. CONN. Pp. 827. Philadelphia: W. B. Saunders Company, 1958. Price, $12.00.

IT is a significant fact that all medical therapy is in a constant state of evolution from year to year, not only by reason of major discoveries and innovations but even more by gradual changes arising from an ever increasing knowledge and understanding of physiology, pharmacology and pathology. This series of annual volumes, therefore, performs a signal service to the practicing physician. The present edition has been prepared by 297 contributors and contains 96 more pages than the last. In many instances several contributors have been invited to write their individual preference in the management of the condition on which they hold divergent opinions. The reader can then exercise his own judgment. The book is highly recommended. R.K.

BILATERAL POLYCYSTIC DISEASE OF THE KIDNEYS. By O. Z. DALGAARD. Translated from the Danish by Harry Cowan, B.Sc. Pp. 253; 39 ills. Copenhagen: Ejnar Munksgaard, 1957.

THIS monograph is a significant contribution to the knowledge of the hereditary aspects of bilateral polycystic disease of the kidneys, as well as a presentation of its clinical aspects and a review of current information on the condition and theories of its origin. The author, by searching the records of hospitals and departments of pathology and one private clinic in which such cases have been especially studied, found a series of 232 patients whose families he was able to study. He discovered an additional 108 family members with a confirmed diagnosis and 52 with a suspected diagnosis of polycystic kidneys. The various clinical, laboratory and radiological studies performed in these individuals are reported in detail. R.K.

LABORATORY MEDICINE: HEMATOLOGY. By JOHN B. MIALE, M.D., Professor of Pathology, University of Miami School of Medicine. Pp. 735; 192 ills. and 9 plates, 5 in color. St. Louis: C. V. Mosby Co., 1958. Price, $13.75.

THIS volume on Hematology is the first of a projected series of texts which are designed to present the laboratory aspects of medicine to medical students and physicians. In general, this work achieves its purpose quite well in that it is well organized, clearly written, and well illustrated. The color plates, however, leave much to be desired. Moreover, the reviewer cannot pass without comment the photograph (Fig. 20, p. 102) used to illustrate sternal bone-marrow aspiration. It depicts the needle imbedded in a hairy, unshaven chest which cannot be accepted as the best of technique. Fortunately, the author does suggest later within the text that "in males, it is best to shave a small area around the site of puncture."

The above criticisms, however, are minor when one considers the over-all excellence of this book. Physicians and medical students will find it a valuable textbook of laboratory hematology. C.Z.

FORENSIC MEDICINE. By KEITH SIMPSON, M.D. (LOND.), Reader in Forensic Medicine to the University of London at Guy's Hospital, London. 3rd ed. Pp. 352; 138 ills. London: Edward Arnold, Ltd., 1958 (The Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $7.00.

THIS is a concise, well written presentation of the essentials of legal medicine and toxicology in the realm of the coroner's physician and from a British viewpoint. As the author states, there have been significant relaxations in British law in regard to sex behavior, drunkenness, addiction to drugs and criminal insanity, with consequent sharp increase in crimes in related categories. This has made it necessary largely to re-write this third edition to bring it in accord with current law and present-day experience in unnatural or violent death. Part I deals with Forensic Medicine. Its chapters discuss signs of death, postmortem changes, identification, types of injuries and wounds, asphyxiation, infanticide, sexual offenses and other aspects of scientific

criminal investigation and court procedure. Part II is on Toxicology with considerations of the types of poisons and poisonings encountered by the medico-legal expert, with due space allotted to the newer synthetic drugs of addiction and to the antihistamines, hypertensives and tranquilizers. There are numerous illustrations, 30 of them new, all of them excellent. Although based on British law and experience, the subject matter is of general significance. The book is an excellent introduction to this subject for medical students and young physicians and is highly recommended. R.K.

A Bibliography of Internal Medicine. Communicable Diseases. By Arthur L. Bloomfield, M.D. Pp. 560. Chicago: The University of Chicago Press, 1958. Price, $10.00.

The tremendous rate of growth of medical literature is responsible for a rapidly increasing ignorance on the part of students and young physicians of the significant writings upon which our modern knowledge is based. This, in turn, limits the perspective of young authors, so that, as Doctor Bloomfield points out, "in current medical writing what is referred to as the 'older literature' often turns out to be that of the previous decade." In this volume the author has performed a signal service for younger and for not-so-young physicians by documenting a series of 30 communicable diseases with well selected abstracts from the important contributions by writers of the past. It is to be hoped that other volumes will follow. R.K.

Alcoholism. By Arnold Z. Pfeffer, M.D., Formerly Associate Clinical Professor of Psychiatry, College of Medicine of New York University. Pp. 98. New York and London: Grune & Stratton, Inc., 1958. Price, $6.50.

This monograph, clearly and concisely written, will serve physicians as a handbook for the management of alcoholic patients. It is especially aimed at the needs of the physician in industry where the occupational features of alcoholism are more easily seen.

Alcoholism is recognized as a disease and psychological factors are central in its etiology. The author considers the medical and neuropsychiatric complications of alcoholism, the psychology of alcoholism and the treatment of this disease. A description of industrial programs for alcoholics is included. The Consolidated Edison-New York University Bellevue Plan is discussed in detail. M.B.

Polysaccharides in Biology. Transactions of the 2nd Conference, April 25, 26 and 27, 1956. Edited by Georg F. Springer, M.D., William Pepper Laboratory of Clinical Medicine and Department of Microbiology, University of Pennsylvania School of Medicine. Pp. 245; 54 ills. New York: Josiah Macy, Jr. Foundation, 1957. Price, $5.00.

This volume contains the transactions of the Second Conference on Polysaccharides in Biology which was held at Princeton, N.J. in April, 1956. As at the preceding conference, a multidiscipline approach was made in connection with these important biologic substances. The principal discussions were grouped about the following topics: Sialic Acid and Related Compounds; Interaction of Polysaccharides and Viruses; Pyrogens; and in a special Appendix certain lipopolysaccharides were considered.

The fundamental nature of these conferences commend them to all who are concerned with basic investigations in this and related areas of biology and medicine. In addition, clinical investigators may find much valuable information pertinent to their respective fields of interest in this and companion volumes. C.Z.

Ward 4: The Mallinckrodt Research Ward of the Massachusetts General Hospital. By James Howard Means, M.D. Pp. 187; 5 ills. Cambridge: Harvard University Press, 1958. Price, $4.50.

"Research" is a word to conjure with, in this day of man-made earth satellites, transistors and miracle drugs. Yet no word is so widely misunderstood, especially in the fields of government and finance, where research is so often thought of as something to buy or subvene at will by fiat or grant. Therefore this little book deserves a wide reading, particularly by laymen, because Dr. Means has written for them a fine description of the tender plant that research really is, and how it must be reared in a proper environment and cared for by an understanding devotee, the researcher (himself a somewhat *rara avis*). The book is the story of the achievements during a span of over 30 years at the Massachusetts General Hospital, in Ward 4, a ten-bed unit with supporting laboratories, by some dedicated workers with inquisitive minds and their cooperative patients

whose medical problems furnished the stimuli for research. R.K.

DERMATOLOGIE UND VENEROLOGIE BAND II, TEIL I. Edited by H. A. GOTTRON UND W. SCHÖNFELD. Pp. 757; 388 ills. Stuttgart: Georg Thieme Verlag, 1958. Price, $41.20.

GOTTRON and Schönfeld have set out to produce a five-volume handbook of Dermatology and Venereology. The present issue is volume II, part I, and deals with the use of various physical modalities in Dermatology, such as physical therapy; special Roentgen therapy; soft Roentgen rays; radium; electrons; radioactive isotopes; ultrasound (sonics?); ultraviolet light; heat; cold; electricity; climate and balneo therapy. There is a section on cosmetic Dermatology and a large one on dermatoses of unknown cause, including among others such processes as erythema multiforme, dermatomyositis, lupus erythematosus, dermatoses of rheumatism, Reiter's disease, and vesiculo-bullous dermatoses (such as pemphigus). There is adequate coverage of the material with excellent illustrations. The use of experts to write up each subject enhances the authoritativeness of the material. The references are numerous and pertinent. H.B.

Morphologische, Biologische und Serologische Eigenschaften der Bartonellen. BY DR. REINHABD WIGAND. Bernhard-Nocht-Institute fur Schiffs-und Tropenkrankheiten, Hamburg, Germany. Pp. 95; 14 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $1.85.

FOR eight years the author has been publishing detailed reports of his studies on the Bartonella organisms. In this paper-bound monograph he has assembled with characteristic German thoroughness what appears to be the significant information available on this subject. The twelve photomicrographs deserve special commendation. E. S.

Analyzing Psychotherapy. BY SOLOMON KATZENELBOGEN, M.D. Pp. 126. New York: Philosophical Library, Inc., 1958. Price, $3.00.

THIS book describes the author's own concept of psychotherapy. It is intended to answer the questions asked of him by his patients. There are very few references to psychiatric or medical literature.

Conciseness and clarity of presentation characterizes the style. The content, quite elementary, is divided into 18 chapters. This book may answer for the layman some questions concerning psychological medicine. M. B.

The Distribution of Radioisotopes of Some Heavy Metals in the Rat. BY PATRICIA W. DURBIN, KENNETH G. SCOTT AND JOSEPH G. HAMILTON. Pp. 34; 9 ills. Berkeley: University of California Press, 1957. Price, $.75.

THIS typically detailed investigation of the distribution of heavy metal isotopes in the rat will be of interest to those involved in studying the toxicity and hazards of these materials; it has no obvious pertinent applications to the clinical sciences. R. R.

Chronicle of The World Health Organization, Vol. 12, No. 3, March, 1958. Pp. 44; 1 ill. Geneva: World Health Organization, 1958. Price, $.30.

Chronicle of The World Health Organization. Vol. 12, No. 4, April, 1958. Pp. 31. Geneva: World Health Organization, 1958. Price, $.30.

Chronicle of The World Health Organization, Vol. 12, No. 5, May, 1958. Pp. 31. Geneva: World Health Organization, 1958. Price, $.30.

Classification of Atherosclerotic Lesions. Report of a Study Group. World Health Organization Technical Report Series No. 143. Pp. 20; 4 ills. Geneva: World Health Organization, 1958. Price, $.30.

Expert Committee on Biological Standardization. Eleventh Report. World Health Organization Technical Report Series No. 147. Pp. 38. Geneva: World Health Organization, 1958. Price, $.30.

De Motu Cordis. BY WILLIAM HARVEY. Translated from the original Latin by Kenneth J. Franklin. Pp. 209; 4 ills. and 1 color plate. Springfield, Ill.: Charles C Thomas, 1957. Price, $3.50.

A CRISP and lively translation of a great medical classic. The Latin text is included for those able to read it, and who wish to check on the translator: for example, to note that *mehercule* is rendered "damme." R.K.

Human Blood in New York City: A Study of Its Procurement, Distribution and Utilization. H. D. KRUSE, M.D., General Director of Study. Pp. 147; illustrated. New York: New York Academy of Medicine, 1958.

A STUDY on the procurement, distribution and utilization of blood in New York City was conducted under the auspices of the New York Academy of Medicine. The findings and recommendations of this group are reported in this small volume which may be of particular interest to those faced with similar problems in their hospital and community blood banks. C.Z.

Lecciones de alergia. BY GUIDO RUIZ MORENO. Pp. 196. Buenos Aires: Lopez & Etchegoyen, 1957.

THIS small volume has been written for the medical student and for physicians other than allergists. It is limited, therefore, to a simple statement of the theory and principles of allergy and its clinical manifestations, their recognition and treatment. The subject matter is well selected, well presented, and, in the main, sound and acceptable. A minor criticism is the lack of references to more detailed discussions of individual topics in the literature, and the erroneous description of the cutaneous method of skin testing as the "scarification" technique. More serious is an undue stress upon prolonged steroid therapy in the treatment of asthma, an all too frequent error in general medical practice.

R.K.

Electrocardiography. BY MICHAEL BERNREITER, M.D., Assistant Clinical Professor of Medicine, University of Kansas. Pp. 134; 92 ills. Philadelphia: J. B. Lippincott Company, 1958. Price, $5.00.

THE author's purpose is to outline "the fundamental aspects of electrocardiography as they are encountered in everyday practice." The book is also meant to supplement graduate courses given by the author. It is inadequate even as an elementary text and inferior to many primers on electrocardiography available in English. The book is not recommended.

The introductory chapter on basic electrical phenomenon consists primarily of five inadequate diagrams. The ionic flux responsible for the action potential is not even mentioned.

The chapter on arrhythmias is composed of a short paragraph on each arrhythmia discussed but not all are even mentioned. The same is true for that on conduction defects. That on ventricular hypertrophy contains information inadequate to help an undergraduate medical student pass an examination on the subject. The last sentence in the book ends with "etc.".

L.S.

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